



Australian Government

Department of Health  
Therapeutic Goods Administration

# Interim scheduling decisions and reasons for decisions by delegates of the Secretary to the Department of Health for matters referred to an advisory committee

5 February 2018

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current *Poisons Standard* and decides to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZK, that the Secretary publish (in a manner the Secretary considers appropriate) the proposed amendment to be referred to an expert advisory committee, the committee to which the proposed amendment will be referred, and the date of the committee meeting. The Secretary must also invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice. Such a notice relating to the interim decisions herein was made available on the [TGA website](#) on 6 September 2017 and closed on 6 October 2017. Public submissions received on or before this closing date will be published on the [TGA website](#) in accordance with regulation 42ZCZL.

Under regulation 42ZCZN of the Regulations, the Secretary, after considering the advice or recommendation of the expert advisory committee, must (subject to regulation 42ZCZO) make an interim decision in relation to the proposed amendment. If the interim decision is to amend the current *Poisons Standard*, the Secretary must, in doing so, take into account the matters mentioned in subsection 52E(1) of the Act (including, for example, the risks and benefits of the use of a substance, and the potential for abuse of a substance) and the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2015), available on the TGA website.

Under regulation 42ZCZP of the Regulations, the Secretary must, among other things, publish (in a manner the Secretary considers appropriate) the scheduling interim decision, the reasons for that decision and the proposed date of effect (for decisions to amend the current *Poisons Standard*, this will be the date when it is expected that the current *Poisons Standard* will be amended to give effect to the decision). These Secretary's interim decisions and reasons related to:

- scheduling proposals initially referred to the November 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS #22);
- scheduling proposals initially referred to the November 2017 meeting of the Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS #17); and
- scheduling proposals initially referred to the November 2017 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #21).

Also in accordance with regulation 42ZCZP of the Regulations, this notice invites the applicants and persons who made a submission in response to the original invitation under paragraph 42ZCZK(1)(d), to make further submissions to the Secretary in relation to the interim decisions within 10 business days after publication of this notice. Further submissions must be relevant to the proposed amendment, must address matters mentioned in section 52E of the Act, and be received by the closing date, **5 March 2018**.

Submissions, preferably in electronic format (word or unsecured PDF), must be received by **5 March 2018** and should be sent to:

- [Chemicals.Scheduling@health.gov.au](mailto:Chemicals.Scheduling@health.gov.au) for items referred to the Advisory Committee on Chemicals Scheduling); or
- [Medicines.Scheduling@health.gov.au](mailto:Medicines.Scheduling@health.gov.au) for items referred to the Advisory Committee on Medicines Scheduling and the Joint Advisory Committee on Medicines and Chemicals Scheduling.

## Privacy and your personal information

Your personal information is protected by law, including the *Privacy Act 1988*. It is collected by the Australian Government Department of Health for the purposes of identifying the person making a submission as part of the public invitation process, and contacting that person about their submission, for example to seek clarification of issues raised in the submissions.

The consequences of not providing your personal information may result in the Department being unable to communicate with you about your submission.

The Department is unlikely to disclose your personal information it has collected as part of the public comment process to any other Department, body or person or to overseas recipients.

More information about the Department's management of personal information is contained in the Department's privacy policy. The Department's privacy policy contains information such as how you may access the personal information the Department holds about you, how you can seek correction of it, and how you may complain about a breach of the Australian Privacy Principles.

The [Department's privacy policy](#) is available on the Department of Health website.

Alternatively, you may contact the Department by telephone on 02 6289 1555 or free call 1800 020 103, or by using the [online enquiries form](#).

# Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service (now Biosecurity)
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia

Abbreviation	Name
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
EU	European Union
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
IUPAC	International Union of Pure and Applied Chemistry

Abbreviation	Name
ISO	International Standards Organization
LC <sub>50</sub>	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD <sub>50</sub>	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
ODA	Office of Devices Authorisation

Abbreviation	Name
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
SPF	Scheduling Policy Framework
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails

Abbreviation	Name
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

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	<p>cross reference: MK-677, NUTROBAL</p> <p>Schedule 4 Appendix D, Part 5</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
<p>alpha-Pyrrolidinovalerophenone (alpha-PVP) and related substances methylone and synthetic cathinones</p>	<p><b>Schedule 9 – New Entry</b> ALPHA-PYRROLIDINOVALEROPHENONE *(ALPHA-PVP).</p> <p><b>Schedule 9 – New Entry</b> METHYLONE *(MDMC).</p> <p><b>Schedule 9 – Amend Entry</b> CATHINONES <b>except</b> when separately specified in these Schedules.</p> <p><b>Index – Amend Entry</b> <b>CATHINONES</b> cross reference: SYNTHETIC CATHINONES</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Ibuprofen	The delegate’s interim decision is that the current scheduling of ibuprofen remains appropriate
Melanotan II	<p><b>Schedule 4 – New Entry</b> MELANOTAN II.</p> <p><b>Index – New Entry</b> <b>MELANOTAN II</b> cross reference: α-MELANOCYTE STIMULATING HORMONE</p> <p>Schedule 4</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Orphenadrine	The delegate’s interim decision is that the current scheduling of orphenadrine remains appropriate.
Clotrimazole	The delegate’s interim decision is that the current scheduling of clotrimazole remains appropriate.

## 1.1 Hyaluronic acid

### ***Referred scheduling proposal***

A delegate from the Therapeutic Goods Administration (TGA) has referred the substance hyaluronic acid for consideration to amend the Schedule 4 entry to include the subclause ‘*for intra-articular injection*’ in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

## ***Scheduling application***

This was a delegate initiated application. The delegate's proposed amendments to the [Poisons Standard](#) are:

### **Schedule 4 – Amend Entry**

HYALURONIC ACID AND ITS POLYMERS in preparations for injection or implantation:

- a) for tissue augmentation;
- b) for cosmetic use;~~or~~
- c) for the treatment of animals; **or**
- d) **for intra-articular injection.**

The delegate's reasons for the request are:

- The use of a product containing hyaluronic acid intended to be used for intra-articular injection for symptomatic treatment of knee osteoarthritis is not specifically noted in the Schedule 4 entry for hyaluronic acid.
- Based on the current schedule entry for hyaluronic acid in the Poisons Standard and on its scheduling history (particularly noting the June 2003 National Drugs and Poisons Schedule Committee (NDPSC) meeting – see [Scheduling History](#) below), hyaluronic acid in a registered product appears to be exempt from scheduling and does not require a prescription.
- According to the Australian Register of Therapeutic Goods (ARTG), the product is a medical device. According to the Appendix A entry for medical devices, medical devices are generally exempt from scheduling. However, this exemption does not extend to the product as it is intended to be used for intra-articular injection for symptomatic treatment of knee osteoarthritis. See subclause e) of the Appendix entry below:

### **Appendix A**

MEDICAL DEVICES classified as Class III by the classification rules set out in Schedule 2 to the Therapeutic Goods (Medical Devices) Regulation 2002, **except:**

- a) injectable tissue reconstructive, augmentation and restoration materials, including collagen;
  - b) medical devices which include anticoagulants;
  - c) artificial tears;
  - d) urinary catheters; or
  - e) intra-articular fluids.
- Sponsors of devices are obliged to ensure that the devices they supply in Australia meet the Australian Essential Principles. Essential Principle 1 of the Medical Devices Regulations 2002 states that:
  - A medical device is to be designed and produced in a way that ensures that:  
*“(a) the device will not compromise the clinical condition or safety of a patient, or the safety and health of the user or any other person, when the device is used on a patient under the conditions and for the purposes for which the device was intended and, if applicable, by a user with appropriate technical knowledge, experience, education or training;”*
  - Schedule 1, Part 2, subsection 13 states that the information supplied with the device (instructions for use) must identify how to use the device safely including having regard to the training and knowledge of potential users of the device. This means that the device itself, or the supplied

instructions for use must clearly state that the device is intended to only be used by an authorised physician.

- The intent of the [Medical Devices Regulations 2002](#) is that the kinds of devices that should only be used by certain health care professionals are only marketed and supplied to these people. XXXX is such a device, as (according its ARTG entry):

*XXXX is intended to be used for intra-articular injection for symptomatic treatment of knee osteoarthritis.*

**Functional description:**

*XXXX is presented in a glass syringe with a rigid tip cap and plunger stopper. The syringe is assembled with a luer lock adapter, finger grip and plunger rod. XXXX is injected into the synovial joint by an authorised person experienced in intra-articular injections following an aseptic technique using an 18 to 22 gauge needle (not supplied). XXXX provides mechanical joint lubrication to the injected joint.*

- Prescriptions are not used for these types of devices, as the product is not supplied directly to the patient but rather to a health care professional who would then directly administer it to the patient. This is unlike a medicine supplied through a prescription, which the patient would obtain themselves using a prescription and then administer it themselves.
- The sponsor of this device (or their agent) should not be marketing this device to a pharmacy that would then supply to the general public.
- The intention of Schedule 4, part c) 'for the treatment of animals' was to allow for the use of hyaluronic acid via intra-articular injection in animals (see June 2003 NDPSC meeting – see [Scheduling History](#) below). The Schedule 4 entry currently excludes this use in humans.

**Current scheduling status**

Hyaluronic acid and its polymers are in Schedule 4 of the current [Poisons Standard](#) as follows:

**Schedule 4**

HYALURONIC ACID AND ITS POLYMERS in preparations for injection or implantation:

- a) for tissue augmentation;
- b) for cosmetic use; or
- c) for the treatment of animals.

**Scheduling history**

The relevant scheduling history of hyaluronic acid is as follows:

*May 1986 National Drugs and Poisons Schedule Committee (NDPSC)*

In May 1986, the NDPSC agreed to include hyaluronic acid in preparations for injection in Schedule 4, on the grounds that the product containing hyaluronic acid was used to treat a serious condition requiring veterinary intervention.

*May 2000 National Drugs and Poisons Schedule Committee (NDPSC)*

In May 2000, the committee were made aware that certain products that contained hyaluronic acid may have been overlooked at the time of registration and were classified as a device.

*February 2001 National Drugs and Poisons Schedule Committee (NDPSC)*

In February 2001, the NDPSC considered a background paper on hyaluronic acid use in devices. The committee had become aware that many products classified as devices for registration purposes, contained scheduled substances. The committee also considered the Trans-Tasman Harmonisation Working Party (TTHWP) recommendation that New Zealand adopt the existing Schedule 4 entry for hyaluronic acid. Additionally, the committee considered a request that the Schedule 4 entry for hyaluronic acid in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) be reviewed, to exempt certain products, containing hyaluronic acid manufactured by bacterial fermentation.

This was deferred until the next meeting to allow assessment of the appropriateness and feasibility of scheduling substances that are either included in products, or are products, regulated as medical devices.

*May 2001 National Drugs and Poisons Schedule Committee (NDPSC)*

In May 2001, the NDPSC agreed that for clarity, the entry for hyaluronic acid in the SUSDP be amended to include its polymers. However, the committee did not agree that injectable products containing hyaluronic acid should not be exempt from scheduling but that these should be subject to the requirements of Schedule 4. The committee agreed to include the entry '*HYALURONIC ACID and its polymers, in preparations for injection.*' in Schedule 4 of the SUSDP, and an entry for intraocular viscoelastic products in Appendix A.

*August 2001 National Drugs and Poisons Schedule Committee (NDPSC)*

In August 2001, the NDPSC considered hyaluronic acid when in intraocular viscoelastic products and confirmed that the Appendix A entry for viscoelastic products remained appropriate.

*February 2002 National Drugs and Poisons Schedule Committee (NDPSC)*

In February 2002, NDPSC considered a proposal to amend the existing entry for hyaluronic acid to read, '*HYALURONIC ACID AND ITS POLYMERS in preparations for injection.*' Members agreed that the proposed amendment to change '*hyaluronic acid and its polymers*' to upper case letters would ensure a consistent interpretation of the entry across the jurisdictions. The committee decided that such an amendment would be appropriate given that there is no regulatory impact expected as a result of the amendment.

*February 2003 National Drugs and Poisons Schedule Committee (NDPSC)*

In February 2003 the NDPSC amended the Schedule 4 entry for hyaluronic acid to include preparations for implantation. The committee agreed to clarify the intent of Schedule 4 entries for substances used in tissue augmentation or cosmetic use (including collagen, hyaluronic acid and polylactic acid), to encompass preparations for injection or implantation. The Schedule 4 hyaluronic acid amendment was made as follows:

HYALURONIC ACID in preparations for injection or implantation:

- a) for tissue augmentation; or
- b) for cosmetic use

*June 2003 National Drugs and Poisons Schedule Committee (NDPSC)*

In June 2003 the NDPSC agreed that the to the Schedule 4 entry amendment for hyaluronic acid inadvertently excluded 4 veterinary products containing sodium hyaluronate for the treatment of non-infectious joint diseases (synovitis) of horses. The committee recognised that the unintended regulatory impact on the Schedule 4 veterinary products and noted that the products required veterinary intervention so should remain in Schedule 4. The committee agreed that the Schedule 4

entry for hyaluronic acid should be amended to include 'c) for the treatment of animals'. The Schedule 4 hyaluronic acid amendment was made as follows:

HYALURONIC ACID in preparations for injection or implantation:

- a) for tissue augmentation; or
- b) for cosmetic use; or
- c) for the treatment of animals.

### ***Australian regulatory information***

According to the [TGA Ingredient Database](#), hyaluronic acid is permitted to be used as an:

- Excipient ingredient in Biologicals, Export Only, Listed Medicines, Over the Counter and Prescription Medicines; and
- Active ingredient in Biologicals, Export Only and Prescription Medicines.

Hyaluronic acid is not currently used in proprietary ingredient (PI) formulation.

Hyaluronic acid is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#) as an excipient in topical medicines for dermal applications.

In the last 30 years, there has been one adverse event reported in the [Database of Adverse Event Notifications – Medicines](#) with hyaluronic acid listed as a single suspected medicine. The reported adverse effect was hypoaesthesia.

There are 2 products on the ARTG containing hyaluronic acid:

- APVMA has 8 products registered for use in horses containing sodium hyaluronate. No adverse events were recorded from January 1995 to December 2013.

### ***International regulations***

#### *Canada*

In Canada, hyaluronic acid for intra articular use is regulated as class III or class IV medical devices and sold as pre-filled single use syringes.

Hyaluronic acid is also permitted for intra-articular use in horses.

#### *United States of America (USA)*

In the USA, hyaluronic acid is permitted for use in intra articular injections, and approved dermal fillers.

Hyaluronic acid is also permitted for intra articular use in horses, subject to conditions of use related to the dosage and treatment regime.

#### *European Union (EU)*

In the EU, there are no apparent restrictions on the use of hyaluronic acid.

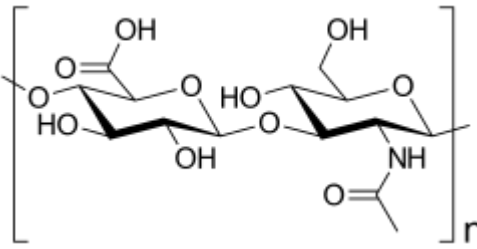
#### *New Zealand (NZ)*

In NZ, hyaluronic acid is considered prescription only for injections or implants for tissue augmentation or cosmetic use, and for general sale for all other uses.

## Substance summary

Hyaluronic acid in its natural form is a linear unbranched (no isomerisation) biological polymer found in all animals, some plants and some bacteria (particularly gram positive). It is a glycosaminoglycan. The hyaluronic acid polymer is composed of repeating units of D-glucuronic acid and N-acetyl-D-glucosamine disaccharide units.

**Table 1.1.1: Chemical properties of hyaluronic acid**

Property	Hyaluronic acid
CAS number	9004-61-9
IUPAC and/or common and/or other names	(2S,4S,5R,6S)-6-[(2S,3R,5S,6R)-3-acetamido-2-[(3S,4R,5R,6R)-6-[(3R,4R,5S,6R)-3-acetamido-2,5-dihydroxy-6-(hydroxymethyl)oxan-4-yl]oxy-2-carboxy-4,5-dihydroxyoxan-3-yl]oxy-5-hydroxy-6-(hydroxymethyl)oxan-4-yl]oxy-3,4,5-trihydroxyoxane-2-carboxylic acid (IUPAC);  Hyaluronan; Hyvisc; Luronit; Vitrax, Amp
Chemical structure	
Molecular formula	Polymer: (C <sub>14</sub> H <sub>21</sub> NO <sub>11</sub> ) <sub>n</sub> Monomer: C <sub>28</sub> H <sub>44</sub> N <sub>2</sub> O <sub>23</sub> , n = 2
Molecular weight	776.7 g/mol (monomer)

N-Acetyl-D-glucosamine is a component of connective tissue, skin, vitreous humour, umbilical cord, synovial fluid and the capsule of certain microorganisms contributing to adhesion, elasticity, and viscosity of extracellular substances. It is also found as small saccharides in the tissue due to enzymatic digestion and chemical breakdown.

Hyaluronan is a commonly term for salts of hyaluronic acid (usually Na, but exists in the tissues as various salts and complexes) but is also used interchangeably with the acid. Hyaluronic acid and its cross-linked derivatives are also used in tissue augmentation and visco-supplementation. Although the cross-linked forms have better residence time, resist enzymatic degradation and could have superior rheological properties in some applications. In literature, the term hylan is used to describe hyaluronic acids cross-linked with highly reactive chemicals (e.g. divinyl sulfone, imides or dialdehyde).

## Pharmacology and Biochemistry

Hyaluronic acid is similar to a substance that occurs naturally in the joints. It may act as a lubricant and shock absorber in the joint, helping the joint to move smoothly.

## Drug indication

Hyaluronic acid is used to treat knee pain in patients with joint inflammation (osteoarthritis). It is usually used in patients who have not responded to other treatments such as paracetamol, exercise, or



physical therapy. Hyaluronic acid may also be used in plastic surgery to reduce wrinkles on the face or as a filler in other parts of the body. It may be used in ophthalmology to assist in the extraction of cataracts, the implantation of intraocular lenses, corneal transplants, glaucoma filtration, retinal attachment and in the treatment of dry eyes and is also used to coat the bladder lining in treating interstitial cystitis.

### *Drug warnings*

Hyaluronic acid is considered to be non-immunogenic and is frequently used for the correction of facial lines. It is believed that hyaluronic acid injection fillers are safe and have no occurrence of serious adverse reactions or allergic reactions. However, publications have documented the rate of intermittent swelling and severe granulomatous allergic reactions that evolved into abscesses. Literature describes a clinical case of a 54-year-old patient.<sup>1</sup> After injection of hyaluronic acid in the treatment of nasolabial folds, palpable painful erythematous nodules evolved into abscesses several months after injection. Surgical treatment and correction of the lesions after the hyaluronic acid injection of the nasolabial folds and histological findings of the erythematous nodules were described. Histological and clinical examination documented intermittent swelling and severe granulomatous allergic reactions that may render the use of hyaluronic acid unacceptable. The reference recommends that patients should be informed of the potential complications when treating facial lines with hyaluronic acid gel.

Non-animal hyaluronic acid gel was developed for soft tissue augmentation and volume expansion and has been reported to offer several advantages in comparison to other augmentation materials. There are rare reports of adverse events believed to be secondary to trace amounts of proteins in the hyaluronic acid raw material. Data from an estimated 144,000 patients treated in 1999 indicated the major reaction to injectable hyaluronic acid was localised hypersensitivity reactions, occurring in approximately 1 of every 1400 patients treated. In 1999, there was an adverse event reported for 1 of every 650 patients (0.15%) treated. These were temporary events that included redness, swelling, localised granulomatous reactions, bacterial infection, as well as acneiform and cystic lesions. In 2000, there was an estimated 262,000 patients treated with hyaluronic acid gel. The total number of adverse events was 144, corresponding to one adverse event for every 1800 patients (0.06%) treated. The major adverse event was again hypersensitivity, occurring in 1 of every 5000 patients treated. According to the reported worldwide adverse events data, hypersensitivity to non-animal hyaluronic acid gel is the major adverse event and is most likely secondary to impurities of bacterial fermentation. According to data from 2000, the incidence of hypersensitivity appears to be declining after the introduction of a more purified hyaluronic acid raw material.<sup>2</sup>

### *Absorption, distribution and excretion*

Hyaluronic acid is absorbed and diffuses slowly out of the injection site. It is eliminated via the canal of Schlemm and is degraded by hyaluronidase enzymes.

### *Mechanism of action*

Hyaluronic acid functions as a tissue lubricant and is thought to play an important role in modulating the interactions between adjacent tissues. Hyaluronic acid is a polysaccharide which is distributed widely in the extracellular matrix of connective tissue. It forms a viscoelastic solution in water which makes it suitable for aqueous and vitreous humor in ophthalmic surgery. Mechanical protection for tissues (iris, retina) and cell layers (corneal, endothelium, and epithelium) are provided by the high viscosity of the solution. Elasticity of the solution assists in absorbing mechanical stress and providing a protective buffer for tissues. This viscoelasticity enables maintenance of a deep chamber during surgical manipulation since the solution does not flow out of the open anterior chamber. In facilitating

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<sup>1</sup> [Honig JF et al.; J Craniofac Surg 14 \(2\): 197-200 \(2003\)](#)

<sup>2</sup> [Friedman PM et al.; Dermatol Surg 28 \(6\): 491-4 \(2002\)](#)



wound healing, it is thought that it acts as a protective transport vehicle, taking peptide growth factors and other structural proteins to a site of action. It is then enzymatically degraded and active proteins are released to promote tissue repair. Hyaluronic acid is being used intra-articularly to treat osteoarthritis. Cell receptors that have been identified for hyaluronic acid fall into three main groups: CD44, Receptor for Hyaluronan-mediated motility (RHAMM) and intracellular adhesion molecule-1 (ICAM-1). CD44 mediates cell interaction with hyaluronic acid and the binding of the two functions as an important part in various physiologic events, such as cell aggregation, migration, proliferation and activation; cell-cell and cell-substrate adhesion; endocytosis of hyaluronic acid, which leads to hyaluronic acid catabolism in macrophages; and assembly of pericellular matrices from hyaluronic acid and proteoglycan. CD44 has two important roles in skin, regulation of keratinocyte proliferation in response to extracellular stimuli and the maintenance of local hyaluronic acid homeostasis. ICAM-1 is known mainly as a metabolic cell surface receptor for hyaluronic acid, and this protein may be responsible mainly for the clearance of hyaluronic acid from lymph and blood plasma, which accounts for perhaps most of its whole-body turnover. Ligand binding of this receptor, thus, triggers a highly coordinated cascade of events that includes the formation of an endocytotic vesicle, its fusion with primary lysosomes, enzymatic digestion to monosaccharides, active transmembrane transport of these sugars to cell sap, phosphorylation of GlcNAc and enzymatic deacetylation. ICAM-1 may also serve as a cell adhesion molecule, and the binding of hyaluronic acid to ICAM-1 may contribute to the control of ICAM-1-mediated inflammatory activation.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACMS advice to the delegate***

The committee recommended that the Schedule 4 entry for hyaluronic acid in the Poisons Standard be amended as follows:

#### **Schedule 4 – Amend Entry**

HYALURONIC ACID AND ITS POLYMERS in preparations for injection or implantation:

- a) ~~for tissue augmentation;~~
- b) ~~for cosmetic use; or~~
- c) ~~for the treatment of animals.~~

The committee also recommends an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 included:

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

- Risks: Hyaluronic acid presents very little risk when used in accordance with TGA-approved Product Information.
- Benefits: The potential benefits are for people not responding to other standard treatments for knee osteoarthritis and also those awaiting joint replacements, etc. Additionally, it is a one-off treatment lasting for 6-9 months rather than having to take increased quantities of pain medication daily. The associated risks of this are especially so in the older population.

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

- For the symptomatic treatment of knee osteoarthritis.
- Potential for misuse.
- The ailments or symptoms that hyaluronic acid is used for require medical intervention.

c) the toxicity of a substance:

- Very low risk of allergy, toxicity or systemic adverse events in humans.

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

- Packaged as an injectable.
- The use of hyaluronic acid requires a specialised medicine delivery device.

e) the potential for abuse of a substance:

- Nil.

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

- Appropriate that hyaluronic acid be administered under a health practitioner's supervision.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

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

### ***Delegate's interim decision***

The delegate's interim decision is to amend the Schedule 4 entry for hyaluronic acid. The proposed Schedule entry is:

#### **Schedule 4 – Amend Entry**

HYALURONIC ACID AND ITS POLYMERS in preparations for injection or implantation.

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

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

- Risks: Hyaluronic acid presents very little risk when used in accordance with TGA-approved Product Information.
- Benefits: The potential benefits are for people not responding to other standard treatments for knee osteoarthritis and also those awaiting joint replacements, etc. Additionally, it is a one-off

treatment lasting for 6-9 months rather than having to take increased quantities of pain medication daily. The associated risks of this are especially so in the older population.

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

- For the symptomatic treatment of knee osteoarthritis.
- Potential for misuse.
- The ailments or symptoms that hyaluronic acid is used for require medical intervention.
- Any use as of an injection or implant requires medical practitioner use.

c) the toxicity of a substance:

- Very low risk of allergy, toxicity or systemic adverse events in humans.

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

- Packaged as an injectable.
- The use of hyaluronic acid requires a specialised medicine delivery device.

e) the potential for abuse of a substance:

- Nil.

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

- Appropriate that hyaluronic acid be administered under a health practitioner's supervision.

## 1.2 Cardarine

### *Referred scheduling proposal*

An application was submitted to create a new entry for cardarine in Schedule 9 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

#### **Schedule 9 – New Entry**

#### **CARDARINE (GW501516).**

The applicant's reasons for the request are:

- Cardarine is known for its experimental status and it is not being approved for human use.
- Cardarine is readily available for purchase in Australia through online suppliers, based in Australia and overseas. It is also available through compounding pharmacies and anti-ageing clinics.
- The lack of regulation allows suppliers to advertise these substances freely and make unproven assertions about the efficacy and safety of the substances. They are administered without reliable advice on appropriate dosage, frequency of administration, and exact content. The products are being positioned as a cutting-edge alternative to steroids on bodybuilding forums and black-market sites.
- The substances are being used by athletes and gym users for the enhancement of sporting performance and aesthetics.

- Scheduling these substances aims to protect public health from the potential adverse impacts of these unapproved substances. The unregulated supply poses potentially serious health concerns. They are administered without reliable advice on appropriate dosage, frequency of administration, and exact content.
- Cardarine may be a potential carcinogen and its effect on humans has not been systematically investigated.
- The Australian Sports Anti-Doping Authority (ASADA) has advised that cardarine has been seized at the border by the Australian Border Force as a prohibited import on multiple occasions.
- If cardarine was marketed, it would require careful regulatory scrutiny. Therefore, in an open, unregulated illicit market, cardarine warrants a listing in the Poisons Standard.
- Cardarine has been identified as a substance of abuse with potential carcinogenic effects, and should be considered for a Schedule 9 entry.

### ***Current scheduling status and relevant scheduling history***

Cardarine is has not previously been considered for scheduling. Therefore, a scheduling history is not available.

### ***Australian regulatory information***

Cardarine is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

### ***International regulations***

#### *World Anti-Doping Agency (WADA)*

Cardarine (GW501516) is a Peroxisome Proliferator Activated Receptor  $\delta$  (PPAR $\delta$ ) agonist. WADA added PPAR $\delta$  agonists to the Prohibited List in January 2009. In 2011, cardarine was placed in the class M3, “gene doping”, based on the following annotation:

*“The use of agents that directly or indirectly affect functions known to influence performance by altering gene expression. For example, peroxisome proliferator activated receptor  $\delta$  (PPAR $\delta$ ) agonists (e.g. GW501516) and PPAR $\delta$ -AMP-activated protein kinase (AMPK) axis agonists (e.g. AICAR) are prohibited”.*

In 2012, cardarine was moved to class S4, “hormone and metabolic modulators”. WADA has undertaken an unprecedented decision to advise athletes about cardarines toxicity. WADA’s aim is to ensure complete awareness of the potential health risks, thus preventing athletes from surrendering to temptation of assuming cardarine for performance improvement.

In March 2013, the WADA published on its website a warning concerning health risks associated with the use of cardarine. It stated that this substance, once a developmental drug, was withdrawn from research and terminated when serious toxicities were discovered in animal subjects (WADA alert, 2013). This was not triggered by new safety data, but by the fact that it was being marketed as a supplement advertised to complement endurance training. As a result, there had been several positive doping tests.

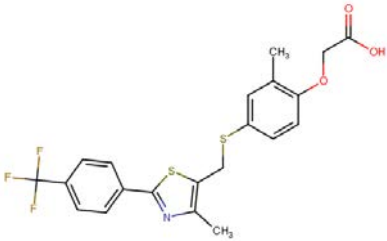
#### *Canada*

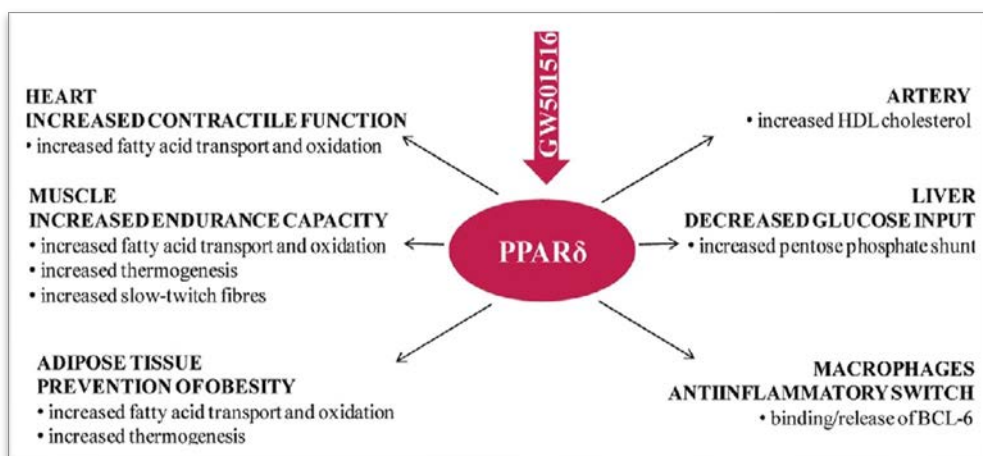
In April 2017, Health Canada issued a [warning to consumers about unauthorised drugs sold online](#), including cardarine. The warning states:

“Cardarine is another drug that is not authorized in Canada for any use. The sarms.ca website also lists cardarine as GW501516. All clinical development of GW501516 was [stopped](#) when toxicities, including various cancers, were discovered following routine, long-term animal studies.”

### Substance summary

**Table 1.2.1: Chemical properties of cardarine (GW-501516)**

Property	Cardarine (GW-501516)
CAS number	317318-70-0
IUPAC and/or common and/or other names	2-[2-methyl-4-[[4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl]methylsulfanyl]phenoxy]acetic acid (IUPAC); GW-501516, GW501516, endurobol, GSK 516
Chemical structure	
Molecular formula	C <sub>21</sub> H <sub>18</sub> F <sub>3</sub> NO <sub>3</sub> S <sub>2</sub>
Molecular weight	453.5 g/mol



**Figure 1.2.1: the effects of cardarine on the nuclear receptor PPAR $\delta$**

Cardarine (GW501516) is a metabolic activator that selectively targets the peroxisome proliferator-activated receptor  $\delta$  (PPAR $\delta$ ) with high affinity and potency thereby rendering it as a PPAR $\delta$  agonist. Other marketed drugs in that class include the thiazolidinediones for treatment of type 2 diabetes mellitus, some of which have had post-marketing safety problems.

Cardarine was primarily developed to treat obesity, diabetes, lipid strain, and heart health problems. Cardarine activates AMP-activated protein kinase, glucose uptake and fatty acid oxidation in skeletal muscle (see Figure 1.2.1). Cardarine may reverse metabolic abnormalities in obese and pre-diabetic individuals by stimulating fatty acid oxidation, burning fat and increasing glucose uptake in skeletal

muscle tissue, which changes the body's metabolism to burn fat for energy instead of muscle or carbohydrates.<sup>3</sup>

Cardarine was initially developed in 1992 by Ligand Pharmaceuticals and GlaxoSmithKline (GSK) as a metabolic agent with potential anti-cancer, anti-obesity and cardiovascular applications. Phase I trials of cardarine for the treatment of hyperlipidaemia began in 2000 followed by phase I/II in 2002. Further development of cardarine was abandoned in 2007 for safety reasons when preclinical toxicology showed that it caused various cancers.<sup>4</sup>

A few clinical trials have been performed on cardarine and its effects on lipid and lipoprotein metabolism. In contrast to the animal toxicity studies, no significant adverse effects were reported in any of the human studies, which may reflect the considerably lower doses administered (up to 10 mg/day) for much shorter periods of time (up to 12 weeks). However, the available clinical data on cardarine's safety is insufficient to claim it is safe for humans. Long-term consequences have not been determined due to the low number of clinical trials performed.

Cardarine has a substantial following in sporting circles. It is also on the WADA Prohibited List under the category S4 'Hormone and Metabolic Modulators' and appears increasingly in the list of drugs linked to anti-doping rule violations.<sup>5</sup>

There are no known side effects associated with cardarine use to date. Unlike most fat loss drugs in use, cardarine does not stimulate the nervous system. There were no side-effects reported in the human studies performed, which may be due to short study durations. It may also be due to the small doses used in humans. The side-effects of cardarine from animal studies including its carcinogenicity potential were based on large doses of the drug.

#### *Limited Human Studies*

A few clinical trials have been performed on cardarine (GW501516) and its effects on lipid and lipoprotein metabolism. In contrast to the animal toxicity studies, no significant adverse effects were reported in any of the human studies, which may reflect the considerably lower doses administered (up to 10 mg/day) for much shorter periods of time (up to 12 weeks). However, the available clinical data on GW501516 safety is insufficient to assess the long-term health risks associated with its intake by human subjects. Long-term consequences have not been discovered yet due to the low number of clinical trials performed.

#### **Summary of clinical trials**

Various clinical trials with cardarine (GW501516) during early drug development are detailed below:

- Phase 1 trial (Clinical trials id [NCT00388180](#))

This was a randomised, double-blind, parallel group study to evaluate the effect of 12-week treatment with GW590735X (20 µg) or GW501516X (10 mg) relative to placebo on measures of adiposity and inflammation in overweight and obese healthy volunteers.

- Phase 1 trial (Clinical trials id [NCT00318617](#))

This was a two part study to separately evaluate the effect of 4-week treatment with GW501516X relative to placebo on cardiac energetics in a randomised, single-blind, repeat dose, parallel group design in healthy male subjects

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<sup>3</sup> Gupta R A, Wang D, Katkuri S, Wang H, Dey SK, DuBois RN(2004) Activation of nuclear hormone receptor peroxisome proliferator-activated receptor-δ accelerates intestinal adenoma growth. *Nat Med* 10(3):245-247.

<sup>4</sup> Geiger LE, Dunsford WS, Lewis DJ, Brennan C, Liu KC, Newsholme SJ (2009). [PS 895 - Rat carcinogenicity study with GW501516, a PPAR delta agonist \(PDF\)](#). 48th Annual Meeting of the Society of Toxicology. Baltimore: [Society of Toxicology](#). p. 105.

<sup>5</sup> Sobolevsky T, Dikunets M, Sukhanova I, Virus E, Rodchenkov G. Detection of PPARδ agonists GW1516 and GW0742 and their metabolites in human urine. *Drug Test Anal.* 2012 Oct;4(10):754-60. Epub 2012 Sep 13. PubMed PMID: 22977012.



This phase I trial was terminated without disclosing the reasons for termination.

- Phase 2 trial (Clinical trials id [NCT00158899](#))

This was a multi-centre, three-staged with interim analyses, parallel, randomised, double-blind, fenofibrate-and placebo-controlled proof of concept and dose-response evaluation of the safety, tolerability, and effects on plasma high-density lipoprotein cholesterol (HDLc) and triglycerides of eight weeks treatment with GW501516 in otherwise healthy patients with low HDLc, mildly to moderately elevated triglycerides, and normal low-density lipoprotein cholesterol (LDLc)

- Phase 4 trial (Clinical trials id [NCT00841217](#))

This was a double-blind randomised crossover trial of 6 week intervention periods to determine whether PPAR-delta agonists (GW501516) had favorable effects on lipoprotein metabolism (2.5 mg/day).

This clinical trial was conducted in Australia (April 2003 to December 2008). The authors concluded that GW501516 increased the hepatic removal of VLDL particles, which might have resulted from decreased apoC-III concentration. GW501516 increased apoA-II production, resulting in an increased concentration of LpA-I: A-II particles. This study elucidates the mechanism of action of this PPAR $\delta$  agonist on lipoprotein metabolism and supports its potential use in treating dyslipidemia in obesity. All these results were achieved without any significant alteration in body weight or insulin resistance. No adverse events were observed.<sup>6</sup>

#### **Eric J. Olson *et al.*, (2012)<sup>7</sup>**

Cardarine (GW501516) (2.5, 5.0, or 10.0 mg) or placebo was given for 12 weeks to patients (n=268) with high-density lipoprotein (HDL) cholesterol <1.16 mmol/L. Fasting lipids/apolipoproteins (apos), insulin, glucose, and free fatty acid were measured; changes from baseline were calculated and assessed. A second smaller exploratory study (n=37) in a similar population was conducted using a sequence of 5 and 10 mg dosing for the assessment of lipoprotein particle concentration. GW501516 produced significant changes in HDL cholesterol, LDL cholesterol, apoA1, and apoB. Fewer very LDL and larger LDL support a transition toward less atherogenic lipoprotein profiles. The doses used were found to be safe with regard to safety outcomes assessed.

#### **Dennis L. Sprecher *et al.*, (2007)<sup>8</sup>**

Healthy volunteers were allocated placebo (n=6) or PPAR $\delta$  agonist (GW501516) at 2.5 mg (n=9) or 10 mg (n=9), orally, once-daily for 2 weeks while hospitalised and sedentary. Standard lipid/lipoproteins were measured and *in vivo* fat feeding studies were conducted. Human skeletal muscle cells were treated with GW501516 *in vitro* and evaluated for lipid-related gene expression and fatty acid oxidation (FAO). Serum TG trended downwards ( $P=0.08$ , 10 mg), whereas TG clearance post fat-feeding improved with drug ( $P=0.02$ ). HDLc was enhanced in both treatment groups (2.5 mg  $P=0.004$ , 10 mg  $P<0.001$ ) when compared with the decrease in the placebo group ( $-11.5\pm 1.6\%$ ,  $P=0.002$ ). These findings complimented *in vitro* cell culture results whereby GW501516 induced FAO and upregulated CPT1 and CD36 expression. No adverse events were identified.

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<sup>6</sup> Ooi, E.M., Watts, G.F., Sprecher, D, Chan, C.F., Barrett, H.H. (2011), 'Mechanism of Action of a Peroxisome Proliferator-Activated Receptor (PPAR)- Agonist on Lipoprotein Metabolism in Dyslipidemic Subjects with Central Obesity', *Journal of Clinical Endocrinology and Metabolism*, 96, 10, pp. E1568-E1576.

<sup>7</sup> Olson EJ, Pearce GL, Jones NP, Sprecher DL. Lipid effects of peroxisome proliferator-activated receptor-d agonist GW501516 in subjects with low high-density lipoprotein cholesterol: characteristics of metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2012; 32: 2289-2294.

<sup>8</sup> Sprecher DL, Massien C, Pearce G, Billin AN, Perlstein I, Willson TM, Hassall DG, Ancellin N, Patterson SD, Lobe DC, Johnson TG. Triglyceride:high-density lipoprotein cholesterol effects in healthy subjects administered a peroxisome proliferator activated receptor delta agonist. *Arterioscler Thromb Vasc Biol.* 2007;27:359-365.

**Nishimura K, et al., (2013)<sup>9</sup>**

Nishimura *et al.*, 2013 conducted a study in Japan to evaluate the foetal and placental developmental toxicity due to cardarine (GW501516) administration to pregnant rats.

In the first experiment, Sprague-Dawley pregnant rats were administered 0, 30 or 100 mg/kg daily dose of GW501516 by gavage from gestational day (GD) 6-17. The current results indicated that maternal oral administration of GW501516 at a dose of 100 mg/kg/day during GD 6 to 17 caused the suppression of maternal body weight and food consumption, and increased foetal death ratio. Placental malformation was also induced by administration of GW501516 at a dose of 100 mg/kg/day. In those placentae, cystic structure was observed in the basal zone. Although the rate of placental malformation was very high (72.2%), placental weight was not affected.

In the second experiment, GW501516 was administered as a single dose of 0, 275 or 350 mg/kg to pregnant rats at gestational days 7, 8,9,10, or 11. One female rat died on GD 9 that was exposed to 350 mg/kg GW501516. Rate of post-implantation loss was significantly higher in the 275 and 350 mg/kg GW501516 groups on GD 9, and 350 mg/kg GW501516 group on GD 10. Single oral administration of GW501516 at a dose of 275 and/or 350 mg/kg on GD 8, 9, 10, or 11 induced placental malformation.

In the third experiment, female Sprague–Dawley rats were administered a single dose of 275mg/kg of GW501516 on gestational day 10. Fetal poor growth was observed. Single oral administration of GW501516 on GD 10 induced cystic degeneration associated with cellular lysis of glycogen cells started from GD 15 in the basal zone.

All results indicate that GW501516 administration is associated with high frequency of placental malformations. GW501516 administration at various dose levels had detrimental effect on foetal survivability and growth.

*Carcinogenicity*

In two abstracts published in *The Toxicologist*, it was shown that when rats and mice were given the drug for two years, there was a significantly increased risk of developing a range of cancers. These carcinogenicity studies were performed as part of the drug approval process.

**L. E. Geiger et al., (2009)<sup>10</sup>**

Carcinogenic potential of cardarine (GW501516) was assessed in male and female Han Wistar rats by daily administration of GW501516 for 104 weeks. Male rats were given a daily dose of 0,5,15 or 30 mg/kg/day for first six months and 0, 5, 20 or 40 mg/kg/day for rest of the study. Female rats were given a daily dose of 0, 3, 10 or 20 mg/kg/day for the entire duration of study.

Neoplastic changes were noted in multiple tissues at all dose levels. Increased mortality was noted in female rats at all dose levels and uterine endometrial carcinoma was the major cause of death in female rats. Other neoplasms related to GW501516 are as follows:

Organ	Neoplasm	Dose level (in mg/kg/day)
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<sup>9</sup> Nishimura K, Nakano N, Chowdhury VS, Kaneto M, Torii M, Hattori M-A, Yamauchi N, Kawai M. Effect of PPAR $\beta/\delta$  agonist on the placentation and embryo-fetal development in rats. *Birth Defects Res B Dev Reprod Toxicol* 2013;98:164–9.

<sup>10</sup> Geiger LE, Dunsford WS, Lewis DJ, Brennan C, Liu KC, Newsholme SJ (2009). [PS 895 - Rat carcinogenicity study with GW501516, a PPAR delta agonist \(PDF\)](#). 48th Annual Meeting of the Society of Toxicology. Baltimore: [Society of Toxicology](#). p. 105.



Liver	Hepatocellular adenoma	10 mg/kg/day
Urinary bladder	Transitional cell carcinoma	20 and 40 mg/kg/day
Thyroid Gland	Follicular cell adenoma	3 mg/kg/day
Thyroid Gland	Follicular cell carcinoma in male rats	20 mg/kg/day
Tongue	Squamous cell papilloma of tongue in male rats	5 and 40 mg/kg/day
Stomach	Squamous cell papilloma in male rats	5 mg/kg/day
	Squamous cell papilloma of stomach in female rats	20 mg/kg/day
	Squamous cell carcinoma of stomach in male rats	40 mg/kg/day
	Squamous cell carcinoma of stomach in female rats	3 mg/kg/day
Skin	Inverted squamous cell papilloma of skin in male rats	5 mg/kg/day
	Inverted squamous cell papilloma of skin in female rats	3 or 20 mg/kg/day
Harderian glands	Adenoma of harderian glands in male rats	5 mg/kg/day
	Adenocarcinoma of harderian glands in male rats	40 mg/kg/day
Testis	Interstitial cell adenoma of testis in male rats	40 mg/kg/day
Ovaries	Sertoli cell adenoma of ovaries in female rats	10 mg/kg/day
Uterus	Polyp and endometrial adenocarcinoma of uterus in female rats	3 mg/kg/day

The authors concluded that some of the tumour types observed in this study have not been reported with either PPAR $\alpha$  or PPAR $\gamma$  agonists and may reflect tumour promotion mediated through PPAR $\delta$  agonism.

**S. J. Newsholme *et al.*, (2009)<sup>11</sup>**

Carcinogenic potential of cardarine (GW501516) was assessed in CD1 mice by daily administration of GW501516 for 104 weeks. The mice were administered a daily dose of 0, 10, 30, 60 or 80 mg/kg/day. Neoplastic changes were noted in multiple tissues at all dose levels. Neoplasms related to GW501516 identified in this study are as follows:

- Hepatocellular carcinoma of liver (dose level 30 mg/kg/day);

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<sup>11</sup> Newsholme SJ, Dunsford WS, Brodie T, Brennan C, Brown M, Geiger LE (2009). [PS 896 - Mouse carcinogenicity study with GW501516, a PPAR delta agonist](#). (PDF). 48th Annual Meeting of the Society of Toxicology. Baltimore: [Society of Toxicology](#). p. 105

- Hepatocellular adenoma of liver (dose level 10 mg/kg/day);
- Squamous cell carcinoma of stomach at all doses; and
- Combined squamous cell tumours *i.e.* squamous cell papilloma and carcinoma and keratoacanthoma at all dose levels.

The results from this study did not support a role of PPAR $\delta$  in colon carcinogenesis, but these results demonstrated an increase in proliferation of certain epithelial cell populations e.g. Squamous cell tumours.

#### **Rajnish A Gupta *et al.*, (2004)<sup>12</sup>**

Gupta *et al.*, 2004 assessed the carcinogenic potential of cardarine (GW501516) by administering it to Apcmin mice. Exposure of Apcmin mice to the PPAR $\delta$  ligand GW501516 resulted in a significant increase in the number and size of intestinal polyps. The most prominent effect was on polyp size; mice treated with the PPAR $\delta$  activator had a fivefold increase in the number of polyps larger than 2 mm. The results implied PPAR $\delta$  in the regulation of intestinal adenoma growth. To test the effects of PPAR $\delta$  activation on polyp growth, Apcmin mice were either given vehicle or 10 mg/kg of GW501516. Treatment was limited to 6 weeks.

The control Apcmin mice developed an average of 30 small intestine polyps and 1.4 colonic polyps. In contrast, GW501516 treatment led to a twofold increase in polyp number in the small intestine, with no change in the large bowel. The authors concluded that PPAR $\delta$  activation promotes the growth of intestinal adenomas in Apcmin mice.

#### **Elizabeth E. Girroir *et al.*, (2007)<sup>13</sup>**

Girroir *et al.*, 2007 examined the effect of ligand activation of PPAR $\delta$  on cell growth of two human cancer cell lines, MCF7 (breast cancer) and UACC903 (melanoma) in the presence or absence of serum using two highly specific PPAR $\delta$  ligands, GW0742 or cardarine (GW501516). Culturing cells in the presence of either GW0742 or GW501516 caused up-regulation of the known PPAR $\delta$  target gene angiopoietin-like protein 4 (ANGPTL4). Inhibition of cell growth was observed in both cell lines cultured in the presence of either GW0742 or GW501516, and the presence or absence of serum had little influence on this inhibition. The authors concluded that ligand activation of PPAR $\delta$  inhibits the growth of both MCF7 and UACC903 cell lines and provide further evidence that PPAR $\delta$  ligands are not mitogenic in human cancer cell lines.

#### **Holly Hollingshead *et al.*, (2007)<sup>14</sup>**

Hollingshead *et al.*, 2007 examined the effect of two different PPAR $\delta$  ligands (GW0742 and GW501516) in human cancer cell lines (HT29, HCT116, LS-174T, HepG2 and HuH7) cultured in the presence or absence of serum and compared *in vitro* analysis with *in vivo* analysis. Neither PPAR $\delta$  ligand increased cell growth nor phosphorylation of Akt and no increase in the expression of VEGF or COX-2 were detected in any cancer cell line in the presence or absence of serum. Similarly, liver, colon and colon polyps from mice administered these PPAR $\delta$  ligands *in vivo* did not exhibit changes in these markers.

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<sup>12</sup> Gupta R A, Wang D, Katkuri S, Wang H, Dey SK, DuBois RN(2004) Activation of nuclear hormone receptor peroxisome proliferator-activated receptor- $\delta$  accelerates intestinal adenoma growth. *Nat Med* 10(3):245-247.

<sup>13</sup> Girroir EE, Hollingshead HE, He P, Billin, A.N., Willson, T.M., Roberston GP, Sharma, A.K., Amin, S., Gonzalez, F.J., Peters, J.M.(2007) Peroxisome proliferator-activated receptor- $\beta/\delta$  (PPAR $\beta/\delta$ ) ligands inhibit growth of UACC903 and MCF7 human cancer cell lines. *Toxicology* Volume 243, Issues 1-2, 14 January 2008, Pages 236-243.

<sup>14</sup> Hollingshead, H.E., Killins, R.L., Girroir, E.E., Billin, A.N., Willson, T.M., Sharma, A.K., Amin, S., Gonzalez, F.J., Peters, J.M., 2007a. Peroxisome proliferator-activated receptor (PPAR $\delta$ ) ligands do not potentiate growth of human cancer cell lines. *Carcinogenesis* (2007) 28 (12): 2641-2649

Claire B. Pollock *et al.*, (2010)<sup>15</sup>

Pollock *et al.*, 2010 described a gastric tumour mouse model that is dependent on the potent and highly selective PPAR $\delta$  agonist cardarine (GW501516) following carcinogen administration. The progression of gastric tumorigenesis was rapid as determined by magnetic resonance imaging and resulted in highly metastatic squamous cell carcinomas of the fore-stomach within two months. Tumorigenesis was associated with gene expression signatures indicative of cell adhesion, invasion, inflammation, and metabolism. Increased PPAR $\delta$  expression in tumours correlated with increased PDK1, Akt,  $\beta$ -catenin, and S100A9 expression. It is important to note that the dose of GW501516 used in the present study is equivalent to daily oral doses of 3–10 mg/kg that were previously shown to specifically enhance PPAR $\delta$ -dependent fatty acid oxidation in mice in previous studies. In addition, PPAR $\delta$  agonist GW7042, which is almost identical to GW501516 in structure, potency, and specificity, was inactive in inducing gene expression in PPAR $\delta$  knockout mice.

### ***Current use pattern in Australia***

An internet search for “GW501516” or “cardarine” indicates that cardarine is sold online as oral liquid, capsule or powder for performance enhancement.

Labels indicate the following:

- Relevant identified uses: “For research purposes only”, “SARM (Selective Androgen Receptor Modulator)”, “For laboratory and research use only”, “Dietary supplement”, “Promotes lean mass” “Anabolic enhancement agent”, “Increases endurance” “CardioCapacity boost” “AMPk booster” “Works with or without exercise” “Endurance enhancer” “Melts body fat” “Weight loss/Endurance”;
- Population: It should ONLY be used by men and women over 21 years old. It is NOT meant for children, teenagers, and pregnant or nursing women;
- Formulation: liquid and powder;
- Route: Oral;
- Dosage: 10-30 mg/day; and
- Intended duration of use: 4-8 weeks taking at least 4 weeks off in between cycles.

### ***Medical Use***

Cardarine was developed to treat obesity, diabetes, lipid strain, and heart health problems. It has been reported to reverse metabolic abnormalities in obese and pre-diabetics by stimulating fatty acid oxidation. Burning fat by increasing glucose uptake in skeletal muscle tissue, this changes metabolism to burn fat for energy instead of muscle or other carbohydrates.

### ***Performance-enhancing use***

Concerns were raised prior to the [2008 Beijing Olympics](#) that cardarine could be used by athletes as an [ergogenic performance-enhancing drug](#) that was not then controlled by regulations or detected by standard tests. Consequently, a urine test to detect cardarine was developed and made available to the [International Olympic Committee](#). The [World Anti-Doping Agency](#) (WADA) developed a test for cardarine and other related [PPAR \$\delta\$](#)  modulators, and added such drugs to the prohibited list in 2009.

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<sup>15</sup> Pollock C B, Rodriguez O, Martin P L, Albanese C, Li X, Kopelovich L, Glazer R I (2010) Induction of Metastatic Gastric Cancer by Peroxisome Proliferator-Activated Receptor $\delta$  Activation *PPAR Res.* 2010; 2010: 571783.

Cardarine has been promoted on [bodybuilding](#) and athletics websites. In 2011 it was reported to cost \$1000 for 10 g. In 2012, WADA re-categorised cardarine from a [gene doping](#) compound to a "hormone and metabolic modulator".

A number of athletes have tested positive for cardarine in the last few years.

### ***Pre-meeting public submissions***

One (1) submission was received that opposed the proposal for cardarine, instead suggesting that a Schedule 9 entry may be more appropriate. The main points opposed to a Schedule 4 entry and in support of a Schedule 9 entry were:

- These medicines are used to alter gene expression and can be used as a physical performance enhancer.
- Clinical evidence of purported health outcomes such as reduced obesity and diabetes through altering gene expression is scant, of low quality and only produced in mice subjects.<sup>16</sup> Human studies of this medicine have not been published.

The public submission will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that new entries in Schedule 10 and in the index be created for cardarine as follows:

#### **Schedule 10 – New Entry**

**CARDARINE.**

#### **Index – New Entry**

**CARDARINE**  
**Schedule 10**

The committee also recommends an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the advice included:

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

- Risks: Cardarine is banned from use as a performance enhancement substance in sports. Demonstrated risks based on the results of animal toxicological studies include carcinogenicity. Development of the drug was abandoned based on the results of toxicological data from animal studies. It has no approved or regulated use. There is very little data available on long-term use in humans. There is reported misuse and inappropriate use by athletes/fitness/gym users, some of whom access cardarine through “black market” channels.
- Benefits: There have been no clearly substantiated benefits based on clinical data or scientific evidence. Cardarine was initially trialled in a small number of early phase trials for potential

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<sup>16</sup> Sprecher DL. (2007). Lipids, lipoproteins, and peroxisome proliferator activated receptor-delta. *Am. J. Cardiol.* 100 (11 A): n20–4.

uses in dyslipidaemia, obesity and diabetes. Limited data show that cardarine has an effect on PPAR $\delta$  receptors, with effects on skeletal muscle, fat and glucose metabolism.

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

- Cardarine was developed as a therapeutic agent and abandoned due to toxicity issues most likely related to its mechanism of action.
- Nil approved uses – there are no products registered on the ARTG containing cardarine. There is no established therapeutic value.
- Various websites claim that cardarine can enhance athletic performance, hence the marketing of cardarine to gyms and the bodybuilding scene. Athletes use it as an endurance booster based on its limited clinical and experimental data. Presently, its use appears to be limited to internet purchases, anti-ageing clinics and compounding pharmacies; possible availability through gyms etc.
- Cardarine is on the WADA prohibited list.

*c) the toxicity of a substance:*

- Cardarine is associated with a higher rate of numerous cancers and a high frequency of reproductive toxic effects in preclinical settings.
- Toxicity has been evaluated in long-term animal studies, showing an increase in tumour formation. These animal studies (usually performed in parallel with early clinical development) resulted in termination of the clinical development program.
- The increase in tumour development was not replicated in the early human studies, which used lower doses and shorter study duration, so long-term effects in humans are unknown.

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

- Nil approved products or accepted dosages.
- Cardarine is available via internet purchase. It is frequently referred to as “Endurobol” and is available as oral liquid, capsule or powder for performance enhancement. Dosage is reported to be 10-30 mg/day and intended for use in cycles of 4-8 weeks on and at least 4 weeks off between cycles.

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

- There is evidence of abuse in ergogenic settings, based on its pharmacological properties, to assist with weight loss and endurance. There are no known documented reports of dependence.
- Its use has been detected following testing of athletes.

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

- Cardarine satisfies SPF factors of a Schedule 10:
  - 1) Cardarine poses a potential public health risk as a result of its sale, possession or supply that requires management. The potential health risk does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.
  - 2) Cardarine has a public health risk that substantially outweighs the benefit to the extent that no schedule would provide appropriate public access to any proposed or known products.

***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS 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 include cardarine in Schedule 10. The proposed Schedule entry is:

#### **Schedule 10 – New Entry**

CARDARINE.

#### **Index – New Entry**

**CARDARINE**  
Schedule 10

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- Risks: Cardarine is banned from use as a performance enhancement substance in sports. Demonstrated risks based on the results of animal toxicological studies include carcinogenicity. Development of the drug was abandoned based on the results of toxicological data from animal studies. It has no approved or regulated use. There is very little data available on long-term use in humans. There is reported misuse and inappropriate use by athletes/fitness/gym users, some of whom access cardarine through “black market” channels.
- Benefits: There have been no clearly substantiated benefits based on clinical data or scientific evidence. The substance was initially trialled in a small number of early phase trials for potential uses in dyslipidaemia, obesity and diabetes. Limited data show that cardarine has an effect on PPAR $\delta$  receptors, with effects on skeletal muscle, fat and glucose metabolism.

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

- Cardarine was developed as a therapeutic agent and abandoned due to toxicity issues most likely related to its mechanism of action.
- Nil approved uses – there are no products registered on the ARTG containing cardarine. There is no established therapeutic value.
- Various websites claim that cardarine can enhance athletic performance, hence the marketing of cardarine to gyms and the bodybuilding scene. Athletes use it as an endurance booster based on its limited clinical and experimental data. Presently, its use appears to be limited to internet purchases, anti-ageing clinics and compounding pharmacies; possible availability through gyms etc.
- Product is on the WADA prohibited list.



c) the toxicity of a substance:

- Cardarine is associated with a higher rate of numerous cancers and a high frequency of reproductive toxic effects in preclinical settings.
- Toxicity has been evaluated in long-term animal studies, showing an increase in tumour formation. These animal studies (usually performed in parallel with early clinical development) resulted in termination of the clinical development program.
- The increase in tumour development was not replicated in the early human studies, which used lower doses and shorter study duration, so long-term effects in humans are unknown.

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

- Nil approved products or accepted dosages.
- Cardarine is available via internet purchase. It is frequently referred to as “Endurobol” and is available as oral liquid, capsule or powder for performance enhancement. Dosage is reported to be 10-30 mg/day and intended for use in cycles of 4-8 weeks on and at least 4 weeks off between cycles.

e) the potential for abuse of a substance:

- There is evidence of abuse in ergogenic settings, based on its pharmacological properties, to assist with weight loss and endurance. There are no known documented reports of dependence.
- Its use has been detected following testing of athletes.

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

- Cardarine satisfies SPF factors of a Schedule 10:
- Cardarine poses a potential public health risk as a result of its sale, possession or supply that requires management. The potential health risk does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.
- Cardarine has a public health risk that substantially outweighs the benefit to the extent that no schedule would provide appropriate public access to any proposed or known products.

## 1.3 Stenabolic (SR9009)

### *Referred scheduling proposal*

An application was submitted to include stenabolic (SR9009) and synthetic REV-ERB agonists in Schedule 9 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

This was a general application. The applicant’s proposed amendments to the [Poisons Standard](#) are:

#### **Schedule 9 – New Entry**

**STENABOLIC (SR9009) & other synthetic REV-ERB agonists, including SR9011, GSK2945, GSK0999, GSK5072 and GSK2667.**

The applicant’s reasons for the request are:

- Apply for a grouped REV-ERB agonists schedule entry to cover all related compounds, including SR9011, GSK2945, GSK0999, GSK5072 and GSK2667. These substances should be considered as

Schedule 9 poisons due to their potential to produce toxic side-effects and potential for misuse and abuse in sports doping.

- Stenabolic (SR9009) (and its related compounds) has not been widely tested for safety in humans. Much of the available research to date is in pre-clinical animal models. These studies suggest that SR9009 and other synthetic REV-ERB agonists can alter the circadian rhythm in rodents (and likely to do this in humans) which has implications for sleep, metabolic issues and potentially mental health problems.
- Scheduling of stenabolic aims to protect public health from the potential adverse impacts of these unapproved substances. The supply of stenabolic products poses health concerns as they are being administered without appropriate trials in humans, without guidelines for the appropriate dosages and frequency of dosages and without knowledge of the exact contents of the product being administered.
- SR9009 and its related compounds are currently sold online as 'workout in a pill' type drugs and other derivatives. It has the potential to enter the Australian market in this space.
- Despite the experimental status of these products they are readily available for purchase in Australia through online suppliers, based in Australia and overseas, and through compounding pharmacies and anti-ageing clinics.
- The lack of regulation allows suppliers to advertise products with stenabolic freely and make unproven assertions about the efficacy and safety of the substances. On bodybuilding forums and black-market sites, stenabolic is being positioned as a cutting-edge alternative to steroids.
- The substances are being used by athletes and gym users for the enhancement of sporting performance and aesthetics.
- Stenabolic may be a potential carcinogen and its effect on humans has not been systematically investigated.
- The Australian Sports Anti-Doping Authority (ASADA) has advised that stenabolic has been seized at the border by the Australian Border Force as prohibited imports on multiple occasions.
- Stenabolic is also prohibited under the World Anti-Doping Agency (WADA) Prohibited List category S4 'Hormone and Metabolic Modulators'.

### ***Current scheduling status and relevant scheduling history***

Stenabolic has not previously been considered for scheduling. Therefore, a scheduling history is not available.

### ***Australian regulatory information***

Cardarine is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

### ***International regulations***

#### *The World Anti-Doping Agency*

Stenabolic is also prohibited under the World Anti-Doping Agency (WADA) Prohibited List category S4 Hormone and Metabolic Modulators.

According to a respected endocrinologist, Stenabolic is captured as a prohibited substance under WADA's Prohibited List category S4 Hormone and Metabolic Modulators and its potent and diverse pharmacological effects warrant its listing on the Poisons Standard. Direct inquiries with WADA regarding prohibited status have been less definitive. WADA advised that this will be a specific item of

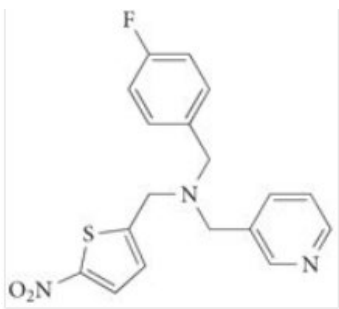
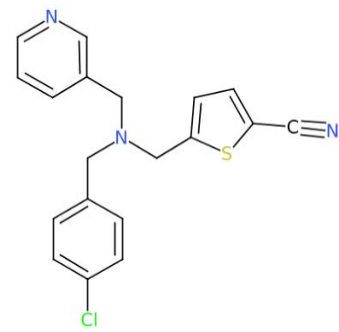


consideration for the prohibited list expert group on 24-25 August 2017, where further advice will be provided. Regardless of this further consideration, and as other derivatives have the potential to enter the Australian market, it is requested that a class entry for synthetic REV-ERB agonists be considered for Schedule 9 with additional separate entries for SR9011, GSK2945, GSK0999, GSK5072 and GSK2667.

### Substance summary

**Table 1.3.1: Chemical properties of synthetic REV-ERBs**

Chemical	CAS number	IUPAC and/or common and/or other names	Structure
Stenabolic	1379686-30-2	ethyl 3-[[[4-chlorophenyl)methyl-[(5-nitrothiophen-2-yl)methyl]amino]methyl]pyrrolidine-1-carboxylate (IUPAC);  1S/C20H24ClN3O4S/c1-2-28-20(25)23-10-9-16(13-23)12-22(11-15-3-5-17(21)6-4-15)14-18-7-8-19(29-18)24(26)27/h3-8,16H,2,9-14H2,1H3 (InChI);  SR9009	
SR9011	1379686-29-9	3-[[[4-chlorophenyl)methyl-[(5-nitrothiophen-2-yl)methyl]amino]methyl]-N-pentylpyrrolidine-1-carboxamide (IUPAC);  1S/C23H31ClN4O3S/c1-2-3-4-12-25-23(29)27-13-11-19(16-27)15-26(14-18-5-7-20(24)8-6-18)17-21-9-10-22(32-21)28(30)31/h5-10,19H,2-4,11-17H2,1H3,(H,25,29) (InChI);	
GSK2945	1438071-12-5	N-[[[4-chloro-2-methylphenyl)methyl]-1-(4-chlorophenyl)-N-[(5-nitrothiophen-2-yl)methyl]methanamine (IUPAC);  1S/C20H18Cl2N2O2S/c1-14-10-18(22)7-4-16(14)12-23(11-15-2-5-17(21)6-3-15)13-19-8-9-20(27-19)24(25)26/h2-10H,11-13H2,1H3 (InChI);	

GSK0999	N/A	N/A	
GSK5072	1438071-23-8	5-[[[4-chlorophenyl)methyl-(pyridin-3-ylmethyl)amino]methyl]thiophene-2-carbonitrile (IUPAC);  1S/C19H16ClN3S/c20-17-5-3-15(4-6-17)12-23(13-16-2-1-9-22-11-16)14-19-8-7-18(10-21)24-19/h1-9,11H,12-14H2 (InChI);	
GSK2667	N/A	N/A	N/A

Stenabolic (SR9009) was developed as an orally active REV-ERB $\alpha$  ligand acting on a heme regulated, nuclear receptor. A non-exclusive list of its pharmacological actions of SR9009 and other synthetic REV-ERB agonists suggests they alter the circadian rhythm in rodents (and likely to do this in humans), which has implications for sleep, metabolic issues and potentially mental health problems.<sup>17</sup>

Stenabolic and its related compounds have not been widely tested for safety in humans. Despite this lack of testing, it is being sold online with a wide range of unsupported health claims.

Stenabolic is an agonist of the orphan receptors REV-ERB $\alpha$  and REV-ERB $\beta$ .<sup>18</sup> The alpha isoform is encoded by the complementary DNA/RNA strand of the *ERBA* oncogene, while the beta isoform is encoded by the template strand within the same chromosome. These receptors are constitutive repressors of transcription through their binding to co-repressors (e.g. nuclear receptor co-repressor 1).

REV-ERB co-repressor binding activity leads to repression of target chromosomal sequences *via* DNA response elements through histone deacetylation and chromatin condensation. Heme is an endogenous ligand required for REV-ERB recruitment of the co-repressor, with the redox state of the iron centre and diatomic gases such as nitric oxide influencing co-repressor binding and hence downstream activity.

REV-ERB receptors are widely expressed throughout the body and have a circadian pattern of expression that reflects their role in circadian transcription regulation. The expression of REV-ERBs and the transcription activator 'retinoic acid receptor-related orphan receptor' (ROR) are 12 hours out of phase with one another, with their influence on transcription of the core mammalian circadian proteins 'brain and muscle ARNT-like 1' (BMAL1) and 'circadian locomotor output cycles protein kaput' (CLOCK) reinforcing core circadian oscillation. REV-ERB $\alpha$  expression is itself regulated by

<sup>17</sup> Solt, L. A., Wang, Y., Banerjee, S., Hughes, T., Kojetin, D. J., Lundasen, T., Shin, Y., Liu, J., Cameron, M. D., Noel, R., Yoo, S.-H., Takahashi, J. S., Butler, A. A., Kamenecka, T. M. & Burris, T. P. (2012). Regulation of Circadian Behavior and Metabolism by Synthetic REV-ERB Agonists. *Nature*, 485(7396), 62-68 (and Supplementary Material).

<sup>18</sup> Kojetin, D. J. & Burris, T. P. (2014). REV-ERB and ROR nuclear receptors as drug targets. *Nature Reviews Drug Discovery*, 13(3), 197-216.

BMAL1-CLOCK dimers interacting with an E box DNA response element in the promoter region of the REV-ERB sequence.

Circadian rhythms are linked to metabolic regulation, with REV-ERBs consequently playing a crucial role in lipid metabolism. REV-ERB $\beta$  has been demonstrated in mice to be central to regulation of genes involved in fatty acid/lipid absorption, energy expenditure and muscle lipogenesis. REV-ERB $\alpha$  is also central in hepatic glucose metabolism. It regulates expression of gluconeogenic enzymes to modulate blood glucose levels and insulin sensitivity. REV-ERB $\alpha$  is additionally involved in regulating oxidative capacity of skeletal muscle, ensuring adequate mitochondria and oxidative function are maintained. REV-ERB $\alpha$  also appears to have increased expression during adipogenesis, with degradation of the protein at later stages to allow for efficient fat cell development.

REV-ERB $\alpha$  appears to have a role in immune function, demonstrating a regulatory action on macrophage production and release of the pro-inflammatory interleukin-6. As REV-ERBs and RORs typically have opposing roles, it is proposed that REV-ERBs may suppress T<sub>H</sub>17 cell development. Gene knockdown studies have indicated REV-ERB is a key player in the development of atherosclerotic lesions through increasing the development of anti-inflammatory M2 macrophages.

#### *In vitro studies*

Stenabolic is 3-4x fold more potent as an agonist than GSK4112, with a 3x fold greater efficacy in repressing a reporter gene in a luciferase assay (REV-ERB $\alpha/\beta$  IC<sub>50</sub> of 670/800 nM). Stenabolic was found to have high specificity for the REV-ERB receptors over 46 other members of the human nuclear receptor superfamily.<sup>19</sup>

In explants from a transgenic mouse model, stenabolic inhibited activity of the hypothalamic suprachiasmatic nucleus circadian clock, as well as the circadian cycle in fibroblasts, suppressing the amplitude of the circadian oscillations without affecting the period.

#### *In vivo studies*

Only two REV-ERB agonists appear to have been tested *in vivo*: stenabolic & the structurally-related SR9011.

Both stenabolic and SR9011 affect circadian expression of several core clock genes in the hypothalamus of murine subjects (suppression of cryptochrome 2; enhancement of period circadian clock 2; phase shift in BMAL1 and CLOCK expression; and complete elimination of circadian expression of the neuronal PAS domain-containing protein2). Dose-dependent suppression of the REV-ERB target *plasminogen activator inhibitor 1* gene was observed in the liver in response to treatment of mice with various doses over 6 days. Observations obtained when mice were kept under light:dark (12 h:12 h) conditions or complete darkness indicated that the effect of light on the circadian oscillator had a significant effect on the drug action.

In white adipose tissue of mice, a suppression of the circadian expression of genes involved in lipid storage was observed following stenabolic administration, with diglyceride acyltransferases 1 and 2, monoacylglycerol acyltransferase, perilipin 1 and hormone sensitive lipase all suppressed. The related compound SR9011 elicited amplification of the circadian expression of genes in skeletal muscle that are involved in fatty acid oxidation and glycolysis.

These effects are all consistent with the REV-ERB agonist effect of stenabolic.

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<sup>19</sup> Solt, L. A., Wang, Y., Banerjee, S., Hughes, T., Kojetin, D. J., Lundasen, T., Shin, Y., Liu, J., Cameron, M. D., Noel, R., Yoo, S.-H., Takahashi, J. S., Butler, A. A., Kamenecka, T. M. & Burris, T. P. (2012). Regulation of Circadian Behavior and Metabolism by Synthetic REV-ERB Agonists. *Nature*, 485(7396), 62-68 (and Supplementary Material).

### Single-dose toxicity

The only data akin to a single-dose toxicity study derives from the study in C57Bl6 mice performed under non-OECD conditions (i.e. total darkness). A total blood count was performed at the end of the study following a single i.p. dose of 100 mg/kg<sup>-1</sup>. There was no significant difference between control and test subjects (24 per group) for the parameters measured. However, it is noted that for several parameters (white blood cell count, lymphocyte count, monocyte count, haematocrit, mean corpuscular volume and platelet count) the average for one or both groups was below the lower end of historical 95% confidence interval (CI), bringing the validity of methodology for this blood count into question.<sup>20</sup>

### Genotoxicity

The structures of many known synthetic REV-ERB agonists, including stenabolic, contain a 2-nitrothiophene moiety, which is a potential toxicological liability due to carcinogenicity concerns. While specific genotoxicity studies have not been performed on these ligands themselves, there is substantial literature that suggests nitrothiophenes present a carcinogen risk. Only the related REV-ERB agonists GSK5072 and GSK2667 lack the 5-nitro group on the thiophene, replacing it with a 5-cyano group.

Drugs with the nitrothiophene or similar groups are uncommon due to their toxicity. Furazolidone is an example of a drug containing the similar moiety nitrofurans, which in Australia is typically prescribed only to patients with refractory *Helicobacter* infections through the Special Access Scheme.

A 1975 study on the mutagenicity of nitro- and aminoheterocycles that did not meet the OECD 471 guideline on the bacterial reverse mutation test but used similar techniques provides useful data on the likelihood of genotoxicity of these compounds.<sup>21</sup> All nitroheterocycles, including 2-acetyl-5-nitrothiophene; 2-acetoxime-5-nitrothiophene; 2-thiazolyl derivatives of 5-nitrothiophene; 2-quinazolyl derivatives of 5-nitrothiophene; and 2-thiazolyl derivatives of 4-nitrothiophene were mutagenic in *Salmonella typhimurium* Strain TA100.

2-acetyl-5-nitrothiophene; 2-formylamino-4-(5-nitro-2-thienyl)thiazole; 1,2-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(3H)-one; 4-morpholino-2-(5-nitro-2-thienyl)quinazoline; 2-amino-4-(4-nitro-2-thienyl)thiazole; and 2-formylamino-4-(4-nitro-2-thienyl)thiazole were also mutagenic in strain TA98, highlighting that regardless of the nitro substituent being *ortho*- or *meta*- to the heteroatom, mutagenic potential was apparent.

### Carcinogenicity

Several 2-quinazolyl derivatives of 5-nitrothiophene studied by Wang, Muraoka & Bryan (1975) were found to be carcinogenic in rats prior to this subsequent experimentation.<sup>22</sup>

Cohen, Erturk & Bryan (1976) also found that 2-heterocycle-substituted 5-nitrothiophenes induced benign and malignant mammary tumours and intestinal tract sarcomas in Sprague-Dawley rats.<sup>23</sup>

Auer, Nabholz & Baetcke (1990) validates the presumption that the 5-nitrothiophenyl group contained in most known synthetic REV-ERB agonists is a toxicological liability, specifically using this moiety as an example on the assessment of chemical hazards in the presence of limited data.<sup>24</sup>

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<sup>20</sup> Charles River Laboratories International Inc. (2012). C57BL/6 Mouse Haematology.

<sup>21</sup> Wang, C. Y., Muraoka, K. & Bryan, G. T. (1975). Mutagenicity of Nitrofurans, Nitrothiophenes, Nitropyrroles, Nitroimidazole, Aminothiophenes, and Aminothiazoles in *Salmonella typhimurium*. *Cancer Research*, 35, 3611-3617.

<sup>22</sup> Wang, C. Y., Muraoka, K. & Bryan, G. T. (1975). Mutagenicity of Nitrofurans, Nitrothiophenes, Nitropyrroles, Nitroimidazole, Aminothiophenes, and Aminothiazoles in *Salmonella typhimurium*. *Cancer Research*, 35, 3611-3617.

<sup>23</sup> Cohen, S. M., Erturk, E. & Bryan, G. T. (1976). Comparative carcinogenicity of 5-nitrothiophenes and 5-nitrofurans in rats. *Journal of the National Cancer Institute*, 57(2), 277-282 (Abstract only) <https://doi.org/10.1093/jnci/57.2.277>.

### ***Pre-meeting public submissions***

One (1) submission was received that opposed the proposal for stenabolic and other synthetic REV-ERB agonists, instead suggesting that a Schedule 9 entry may be more appropriate. The main points opposed to a Schedule 4 entry and in support of a Schedule 9 entry were:

- These medicines are used to alter gene expression and can be used as a physical performance enhancer.
- Clinical evidence of purported health outcomes such as reduced obesity and diabetes through altering gene expression is scant, of low quality and only produced in mice subjects.<sup>25</sup> Human studies of this medicine have not been published.

The public submission will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that stenabolic (SR9009) and other REV-ERB agonists be included in Schedule 4 and Appendix D, along with cross referencing to similar compounds in the index, as follows:

#### **Schedule 4 – New Entry**

# STENABOLIC (SR9009) and other synthetic REV-ERB agonists.

#### **Appendix D, Part 5 – New Entry**

STENABOLIC (SR9009) and other synthetic REV-ERB agonists.

#### **Index – New Entry**

**STENABOLIC (SR9009) and other synthetic REV-ERB agonists**

cross reference: SR9011, GSK2945, GSK0999, GSK5072, GSK2667

Schedule 4

Appendix D, Part 5

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the advice comprised the following:

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

- Risks: Currently no human safety data for stenabolic and synthetic REV-ERB agonists.
- Benefits: no current benefits.

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

- Currently no established therapeutic use.

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<sup>24</sup> Auer, C. M., Nabholz, J. V. & Baetcke, K. P. (1990). Mode of Action and the Assessment of Chemical Hazards in the Presence of Limited Data: Use of Structure-Activity Relationships (SAR) under TSCA, Section 5. *Environmental Health Perspectives*, 87, 183-197.

<sup>25</sup> Sprecher DL. (2007). Lipids, lipoproteins, and peroxisome proliferator activated receptor-delta. *Am. J. Cardiol.* 100 (11 A): n20–4.

c) the toxicity of a substance:

- Potentially carcinogenic, however details of toxicity are yet to be fully established as there has been no marketing experience in Australia.
- Stenabolic and synthetic REV-ERB agonists have a range of potent pharmacological effects.

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

- Sold as capsules (5-20 mg) or oral liquid (20 mg/mL).
- Currently no guidelines for the appropriate dosages and frequency of dosages.

e) the potential for abuse of a substance:

- Stenabolic and synthetic REV-ERB agonists are being illicitly marketed to athletes and gym users as an alternative to steroids and as an anti-aging, fat-reducing agent.

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

- Nil.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

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

### ***Delegate's interim decision***

The delegate's interim decision is to include stenabolic (SR9009) and other synthetic REV-ERB agonists in Schedule 4 with an Appendix D (Part 5) entry. The proposed Schedule entry is:

#### **Schedule 4 – New Entry**

# STENABOLIC (SR9009) and other synthetic REV-ERB agonists.

#### **Appendix D, Part 5 – New Entry**

STENABOLIC (SR9009) and other synthetic REV-ERB agonists.

#### **Index – New Entry**

#### **STENABOLIC (SR9009) and other synthetic REV-ERB agonists**

cross reference: SR9011, GSK2945, GSK0999, GSK5072, GSK2667

Schedule 4

Appendix D, Part 5

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

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

- Risks: Currently no human safety data for stenabolic and synthetic REV-ERB agonists.
- Benefits: no current benefits.

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

- Currently no established therapeutic use.

c) the toxicity of a substance:

- Potentially carcinogenic, however details of toxicity are yet to be fully established as there has been no marketing experience in Australia.
- Stenabolic and synthetic REV-ERB agonists have a range of potent pharmacological effects.

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

- Sold as capsules (5-20 mg) or oral liquid (20 mg/mL).
- Currently no guidelines for the appropriate dosages and frequency of dosages.

e) the potential for abuse of a substance:

- Stenabolic and synthetic REV-ERB agonists are being illicitly marketed to athletes and gym users as an alternative to steroids and as an anti-aging, fat-reducing agent.

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

- Nil.

## 1.4 Ibutamoren

### ***Referred scheduling proposal***

An application was submitted to create a new entry in Schedule 4 for ibutamoren in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### ***Scheduling application***

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

#### **Schedule 4 – New Entry**

**# IBUTAMOREN.**

#### **Appendix D – New Entry**

**IBUTAMOREN.**

The applicant's reasons for the request are:

- Ibutamoren is an experimental drug that has not been systematically investigated beyond clinical trials.
- Ibutamoren is currently sold online as a 'fountain of youth'-type drug for muscle gain as well as other anecdotal effects. This highlights the potential for misuse and abuse by the sporting community and general public.

- Ibutamoren is a growth hormone secretagogue. It is captured under the broad class entry in Schedule 4 of the Poisons Standard for growth hormone secretagogues in. However, ibutamoren should be considered for an individual entry in Schedule 4 and Appendix D due to its potential for misuse and abuse in sports doping.

### ***Current scheduling status***

Ibutamoren is currently captured by the Growth Hormone Secretagogues (GHSs) listing in Schedule 4 and Appendix D, Part 5 of the Poisons Standard. These and other Performance and Image Enhancing Drugs (PIEDs) are listed as follows:

#### **Schedule 4**

- # CJC-1295 (CAS No. 863288-34-0).
- # PRALMORELIN ((GROWTH HORMONE RELEASING PEPTIDE-2) (GHRP-2)).
- # GROWTH HORMONE RELEASING PEPTIDE-6 (GHRP-6).
- # GROWTH HORMONE RELEASING HORMONES \*(GHRHs).
- # GROWTH HORMONE RELEASING PEPTIDES \*(GHRPs).
- # GROWTH HORMONE SECRETAGOGUES\* (GHSs).
- # HEXARELIN.
- # IPAMORELIN.
- # THYMOSIN BETA 4 (THYMOSIN  $\beta$ 4).
- # TB-500.
- # FIBROBLAST GROWTH FACTORS.

#### **Appendix D, Part 5**

All the substances above are also in Appendix D, Part 5 (as indicated by the #).

### ***Scheduling history***

In November 2014, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal to include new entries for the following performance and image enhancing drugs in Schedule 4 and Appendix D:

- Growth Hormone Releasing Hormones and Analogues (GHRHs);
- Growth Hormone Secretagogues (GHSs);
- Growth Hormone Releasing Peptides (GHRPs); and
- Growth Hormone Variants:
  - CJC-1295 (CAS No. 863288-34-0);
  - Ipamorelin;
  - pralmorelin (growth hormone releasing peptide-2 (GHRP-2));
  - growth hormone releasing peptide-6 (GHRP-6);
  - Hexarelin; and
  - AOD-9604 (CAS No. 221231-10-3).



In March 2015, the ACMS recommended, and the delegate confirmed, that the currently scheduled substances should be included in Schedule 4 and in Appendix D, Item 5 in the Poisons Standard. The reasons for the recommendation were due to several points of safety. These include the long-term safety of PIEDs is not established and their potential adverse effects may include those associated with administration of growth hormones and the potential for downstream health effects such as adverse cardiovascular and hormonal effects. The limited safety data on AOD-9604 do not provide evidence that repeated intravenous or subcutaneous injections are safe or that long term use of oral doses in excess of those used in the clinical trials are safe. Scheduling of the substances would help ensure there is appropriate medical supervision of use and may make the substances more difficult to obtain without a lawful purpose. There is also evidence of involvement of organised crime in supply of the substances. The substances are offered for sale via the internet. Suppliers are making unproven assertions about the efficacy and safety of the substances.

As part of the above considerations, the ACMS also recommended that new Schedule 4 and Appendix D, Item 5 be created for Thymosin Beta 4, TB-500 and fibroblast growth factors. The delegate agreed with the committee and made a final decision on 17 March 2016. Reasons for the delegate's decision include: no form of Thymosin Beta 4 was approved for human therapeutic use anywhere in the world; the substances are considered experimental in humans and are increasingly being used as a performance or image enhancing agent, thus have potential for misuse or abuse; toxicity is unknown due to the experimental nature of the medication but they have potential side effects including carcinogenicity and cardiovascular problems.

### ***Australian regulatory information***

Ibutamoren is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

### ***International regulations***

#### *World Anti-Doping Agency (WADA) Prohibited List*

Ibutamoren is prohibited from sport under the category S2 Peptide hormones, growth factors, related substances and mimetics.

#### *United States of America (USA)*

On 19 June 2017, the USA Food and Drug Administration granted [Orphan Drug Designation](#) for ibutamoren mesylate (MK-0677) for the treatment of growth hormone deficiency.

#### *European Union*

On 20 June 2017, the European Commission granted orphan designation ([EU/3/17/1882](#)) for ibutamoren mesilate (also known as MK-0677) for the treatment of growth hormone deficiency.

#### *New Zealand (NZ)*

In NZ, ibutamoren is currently unclassified.

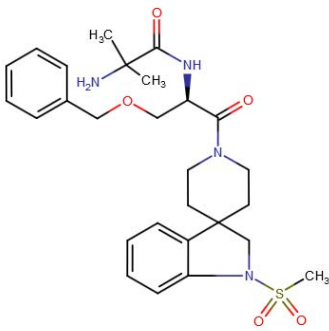
### ***Substance summary***

Ibutamoren is a potent, orally active small molecule (non-peptide) ghrelin analogue which is exploited pharmacologically as a growth hormone (GH) secretagogue. Though there was some interest to market this drug, like virtually all other congeners in this class, their marketing campaigns were mostly abandoned failed due to inadequate efficacy (short-term benefits in GH stimulation and increases in muscle and bone mass proved ill-sustained in longer term studies) and safety concerns.

Ibutamoren is an orally-available growth hormone secretagogue that is functionally indistinguishable both *in vitro* and *in vivo* from the Schedule 4 and Appendix D substance growth hormone-releasing peptide 6 (GHRP-6).<sup>26</sup> The substance was developed as an investigational drug for use in animal models only.

Ibutamoren is a ghrelin receptor agonist. Agonists of the ghrelin receptor are known as growth hormone secretagogues, a class of compounds that resides within Schedule 4 of the Poisons Standard. This receptor leads to stimulation of growth hormone secretion in the same manner as elicited by ghrelin.<sup>27</sup>

**Table 1.4.1: Chemical information of ibutamoren**

Property	Ibutamoren
CAS name	MK-677
CAS numbers	159634-47-6
IUPAC and/or common and/or other names	2-amino-2-methyl-N-[(2R)-1-(1-methylsulfonylspiro[2H-indole-3,4'-piperidine]-1'-yl)-1-oxo-3-phenylmethoxypropan-2-yl]propanamide (IUPAC); Ibutamoren (INN); Common names: Nutrobal; L-163,191; GH pep; Propanamide; crescendo
Chemical structure	 The chemical structure of Ibutamoren is a complex molecule. It features a central piperidine ring. Attached to this ring is a spiro system with a 2H-indole ring. The indole ring has a methylsulfonyl group (-SO2CH3) at the 3-position. Another branch from the piperidine ring is a propanamide chain. This chain has a methyl group and an amino group (-NH2) on the alpha carbon, and a 2-phenylmethoxy group (-OCH2C6H5) on the beta carbon. The amide group is at the end of the propanamide chain.
Molecular formula	C <sub>27</sub> H <sub>36</sub> N <sub>4</sub> O <sub>5</sub> S
Molecular weight	528.7 g/mol

### **Pre-meeting public submissions**

No submissions were received.

<sup>26</sup> Patchett, A. A.; Nargund, R. P., Tata, J. R., Chen, M.-H., Barakat, K. J., Johnston, D. B. R., Cheng, K., Chan, W. W.-S., Butler, B., Hickey, G., Jacks, T., Schleim, K., Pong, S.-S., Chaung, L.-Y. P., Chen, H. Y., Frazier, E., Leung, K. H., Chiu, S.-H. L. & Smith, R. G. (1995). Design and biological activities of L-163,191 (MK-0677): A potent, orally active growth hormone secretagogue. Proceedings of the National Academy of Sciences of the USA, 92, 7001-7005.

<sup>27</sup> Cassoni, P., Papotti, M., Ghe, C., Catapano, F., Sapino, A., Graziani, A., Deghenghi, R., Reissmann, T., Ghigo, E. & Muccioli, G. (2001). Identification, Characterization, and Biological Activity of Specific Receptors for Natural (Ghrelin) and Synthetic Growth Hormone Secretagogues and Analogs in Human Breast Carcinomas and Cell Lines. Journal of Clinical Endocrinology and Metabolism, 86(4), 1738-1745.

## **Summary of ACMS advice to the delegate**

The committee recommended that new Schedule 4 and Appendix D entries be created for ibutamoren in the Poisons Standard, along with a cross reference to similar compounds in the index, as follows:

### **Schedule 4 – New Entry**

# IBUTAMOREN.

### **Appendix D, Part 5 – New Entry**

IBUTAMOREN

### **Index – New Entry**

**IBUTAMOREN**

cross reference: MK-677, Nutrobal

Schedule 4

Appendix D, Part 5

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the advice comprised the following:

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

- Risks: long term safety of ibutamoren has not been established but some safety signals have been detected in clinical trials.
- Benefits: theoretical benefits on muscle and bone accrual have not been confirmed in clinical trials. There are no long-term safety data. At least one well designed Phase IIb trial of ibutamoren was terminated early due to a signal of congestive heart failure (Adunsky A *et al.*, Arch Gerontol Geriatr 2011).

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

- Ibutamoren is widely promoted for uses other than what it had been originally trialled, i.e. for acute illness, post-op and hip fracture recovery.
- Ibutamoren is used illicitly to increase muscle mass, predominantly in the context of athletic and aesthetic pursuits.

c) the toxicity of a substance:

- Toxicity of ibutamoren remains unknown, but concerns exist (see point (a)).

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

- Ibutamoren is available online as an oral powder. There are also capsules and liquid formulations apparently available.

e) the potential for abuse of a substance:

- Ibutamoren is advertised online as an ‘anti-ageing’, ‘fountain of youth’ product.
- Potential for abuse and misuse in sports doping is high.

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

- Evidence that ibutamoren products are marketed as a safe, oral alternative to other performance enhancing drugs.
- Oral presentation may have a lower barrier to use than agents requiring injection.
- This substance is already covered by the group entry of Growth Hormone Secretagogues. However, a specific entry is required to ensure clarification of its scheduling status.

**Delegate's considerations**

The delegate considered the following in regards to this proposal:

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

**Delegate's interim decision**

The delegate's interim decision is to include ibutamoren in Schedule 4 with an Appendix D (Part 5) entry. The proposed Schedule entry is:

**Schedule 4 – New Entry**

# IBUTAMOREN.

**Appendix D, Part 5 – New Entry**

IBUTAMOREN

**Index – New Entry**

**IBUTAMOREN**

cross reference: MK-677, NUTROBAL

Schedule 4

Appendix D, Part 5

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- Risks: long term safety of ibutamoren has not been established but some safety signals have been detected in clinical trials.
- Benefits: theoretical benefits on muscle and bone accrual have not been confirmed in clinical trials. There are no long-term safety data. At least one well designed Phase IIb trial of ibutamoren was terminated early due to a signal of congestive heart failure (Adunsky A *et al.*, Arch Gerontol Geriatr 2011).

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

- Ibutamoren is widely promoted for uses other than what it had been originally trialled, i.e. for acute illness, post-op and hip fracture recovery.
- Ibutamoren is used illicitly to increase muscle mass, predominantly in the context of athletic and aesthetic pursuits.

c) the toxicity of a substance:

- Toxicity of ibutamoren remains unknown, but concerns exist (see point (a)).

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

- Ibutamoren is available online as an oral powder. There are also capsules and liquid formulations apparently available.

e) the potential for abuse of a substance:

- Ibutamoren is advertised online as an ‘anti-ageing’, ‘fountain of youth’ product.
- Potential for abuse and misuse in sports doping is high.

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

- Evidence that ibutamoren products are marketed as a safe, oral alternative to other performance enhancing drugs.
- Oral presentation may have a lower barrier to use than agents requiring injection.
- This substance is already covered by the group entry of Growth Hormone Secretagogues. However, a specific entry is required to ensure clarification of its scheduling status.

## 1.5 alpha-Pyrrolidinovalerophenone (alpha-PVP) and related substances methydone and synthetic cathinones

### *Referred scheduling proposal*

A delegate from the Therapeutic Goods Administration (TGA) has referred the substance alpha-pyrrolidinovalerophenone (alpha-PVP) along with related substances methydone and synthetic cathinones for consideration to create and/or amend Schedule entries in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

This was a delegate initiated application. The delegate’s proposed amendments to the [Poisons Standard](#) are:

#### **Schedule 9 – New Entries**

ALPHA-PYRROLIDINOVALEROPHENONE \*(ALPHA-PVP).

METHYLONE \*(MDMC).

OR

#### **Schedule 4 – New Entries**

# ALPHA-PYRROLIDINOVALEROPHENONE \*(ALPHA-PVP).

# METHYLONE \*(MDMC).

#### **Appendix D, Part 5 – New Entries**

ALPHA-PYRROLIDINOVALEROPHENONE \*(ALPHA-PVP).

METHYLONE \*(MDMC).

Control: 5 (Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)).

AND

#### Schedule 9 – Amend Entry

CATHINONES **except** when separately specified in these Schedules.

OR

#### Schedule 9 or Schedule 4/Appendix D – New Entry

# SYNTHETIC CATHINONES **except** when separately specified in these Schedules.

The delegate's reasons for the request are:

- Synthetic cathinones (also known as substituted cathinones or cathinone derivatives) are derivatives of cathinone, a monoamine alkaloid found in the khat plant (*Catha edulis*), which are often referred to colloquially as “bath salts”. Synthetic cathinones elicit a variety of amphetamine-like and/or 3,4-methylenedioxy-methamphetamine (MDMA)-like physiological, subjective, and behavioural effects.
- Synthetic cathinones act predominantly as central nervous system stimulants. Stimulants mediate the actions of dopamine, norepinephrine and/or serotonin, mimicking the effects of traditional drugs such as cocaine, amphetamine, methamphetamine and ecstasy.
- Cathinone and its related substances have the potential to be misused and abused. Synthetic cathinones include alpha-PVP and methylone.
- Synthetic cathinones are the  $\beta$ -keto ( $\beta$ k) analogues of a corresponding phenethylamine. Cathinone itself is  $\beta$ -keto ( $\beta$ k) amphetamine, 2-aminopropiophenone or, more formally, 2-amino-1-phenyl-1-propanone (IUPAC systematic name). The group includes several substances that have been used as active pharmaceutical ingredients (API) of medicinal products, e.g. amfepramone (diethylpropion).
- Use of synthetic cathinones has been associated with sympathomimetic toxidrome.
- Most of the unregulated cathinone derivatives (synthetic cathinones) that have been marketed in are ring-substituted and first appeared in drug markets in the mid-2000s. The most prevalent of which appears to be mephedrone (4-methylmethcathinone).<sup>28</sup> In 2005, methylone, an analogue of MDMA, was the first synthetic cathinone reported to the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA). In 2007, reports of 4-methylmethcathinone (mephedrone, currently in Schedule 9) use emerged, first in Israel and then in other countries and regions, including Australia, Scandinavia, Ireland and the United Kingdom.<sup>29</sup> Mephedrone was reportedly first synthesised in 1929.<sup>30</sup>
- The most commonly available cathinones sold on the recreational market in the period up to 2010 appear to be mephedrone (captured under the Schedule 9 entry, 4-methylmethcathinone) and

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<sup>28</sup> [The Europe Monitoring Centre for Drugs and Drug Addiction – Synthetic cathinones drug profile](#)

<sup>29</sup> Kelly, J.P. “Cathinone derivatives: A review of their chemistry, pharmacology and toxicology”, *Drug Testing and Analysis* 3 (2011): 439-453.

<sup>30</sup> Saem de Burnaga Sanchez, J. “Sur un homologue de l'ephedrine”, *Bulletin de la Société Chimique de France* 45 (1929): 284-86. [4] Meyer, M.R., Wilhelm, J., Peters, F.T., Maurer, H.H. “Beta-ketone amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone and methylone in urine using gas chromatography-mass spectrometry”, *Analytical and Bioanalytical Chemistry* 396 (2010):1225–1233.

methylone (unscheduled). These products are usually encountered as highly pure white or brown powders. Ring-substituted cathinone derivatives are claimed to have effects similar to those of cocaine, amphetamine or 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), but little is known of their detailed pharmacology.

- Methylone (unscheduled) is one of the most popular products with stimulant effects. Methylone is a synthetic cathinone and an alternative of MDMA. Methylone in most cases is taken orally or by insufflation. Methylone is also part of a party liquid.
- Synthetic cathinones were associated with nearly 23,000 emergency department visits in the United States in 2011,<sup>31</sup> and have been implicated in multiple deaths.<sup>32</sup>

### ***Current scheduling status***

#### *Cathinone*

Cathinone is specifically listed in the [Poisons Standard](#) under Schedule 9 as a single chemical entry, not a class entry as follows:

#### **Schedule 9**

CATHINONE.

#### *alpha-Pyrrolidinovalerophenone (alpha-PVP)*

alpha-PVP, also known as alpha-pyrrolidinopentiophenone, is not specifically listed in the [Poisons Standard](#). It is structurally related to, but not captured by, pyrovalerone (Schedule 4), prolintane (Schedule 4), 3,4-methylenedioxypropylvalerone (MDPV, Schedule 9) and cathinone (Schedule 9).

#### *Methylone*

Methylone is not specifically listed in the [Poisons Standard](#). Methylone is structurally related to, but not captured by, the Schedule 9 entry for MDMA (differing only by a single beta-ketone). Methylone is also chemically related to several other cathinones and amphetamines already included in Schedules 9 and 8.

#### *Related substances listed in the [Poisons Standard](#)*

#### **Schedule 9**

N-ETHYL- $\alpha$ -METHYL-3,4-(METHYLENEDIOXY)PHENETHYLAMINE \*(N-ETHYL MDA).

5-METHOXY-3,4-METHYLENEDIOXYAMFETAMINE \*(MMDA).

3,4-METHYLENEDIOXYAMFETAMINE \*(MDA).

3,4-METHYLENEDIOXYPYROVALERONE \*(MDPV).

N- $\alpha$ -[METHYL-3,4-(METHYLENEDIOXY)PHENETHYL]HYDROXYLAMINE \*(N-HYDROXY MDA).

N,  $\alpha$  -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE \*(MDMA).

N-METHYL-1-(3,4-METHYLENEDIOXYPHENYL)-2-BUTANAMINE \*(MBDB).

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<sup>31</sup> U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality Drug Abuse Warning Network (DAWN). (2013). "[Bath salts" were involved in over 20,000 drug-related emergency department visits in 2011.](#)

<sup>32</sup> Maskell *et al.*, "Mephedrone (4-Methylmethcathinone)-Related Deaths", *Journal of Analytical Toxicology* 35(2011)188-191.



METHCATHINONE.

4-METHYLMETHCATHINONE.

### **Schedule 8**

AMFETAMINE.

DEXAMFETAMINE.

LEVAMFETAMINE.

LEVOMETHAMFETAMINE.

METAMFETAMINE.

### **Schedule 4**

BUPROPION.

PROLINTANE.

PYROVALERONE.

### ***Scheduling history***

#### *alpha-PVP*

alpha-PVP, also known as alpha-pyrrolidinopentiophenone, has not been previously considered for scheduling. Therefore, a scheduling history is not available.

#### *Cathinone*

In August 1986, the Drugs and Poisons Schedule Committee (DPSC) considered a Schedule 9 entry for cathinone in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) under Psychotropic Substances. It was discussed after a notification from the Secretary-General from the United Nations.

In November 1986, after review of the States and Territories, the DPSC agreed to add cathinone into Schedule 9 of the SUSDP.

#### *Methcathinone*

In November 1998, the National Drugs and Poisons Schedule Committee (NDPSC) agreed to the inclusion of methcathinone in Schedule 9 due to its potential as a problem drug.

#### *Methylone*

Methylone has not been previously considered for scheduling. Therefore, a scheduling history is not available.

#### *4-Methylmethcathinone (mephedrone)*

In June 2010, the NDPSC decided to create a new entry in Schedule 9 for 4-methylmethcathinone (mephedrone). The committee agreed that 4-methylmethcathinone, as a derivative of methcathinone, is captured by the Schedule 9 entry for methcathinone. The committee further agreed that it would be appropriate to create a new entry for 4-methylmethcathinone in Schedule 9 to clarify that this substance is indeed a prohibited substance.

### *3,4-methylenedioxypropylamphetamine (MDPV)*

In October 2011, the Advisory Committee on Medicines Scheduling (ACMS) considered an application to include MDPV in Schedule 9 of the Poisons Standard due to it being structurally related to cathinone and MDMA. The ACMS recommended that MDPV be included in Schedule 9, with a cross-reference to 3,4-methylenedioxypropylamphetamine, due to its potency and its associated dangers with heavy and repetitive use.

### ***Australian regulatory information***

Alpha-PVP, methylone and cathinone are not an excipient or active in any medicines on the [ARTG](#).

According to the [TGA Ingredient Database](#), prolintane is available for use as an:

- Active ingredient in biologicals, export only and prescription medicines;
- Excipient ingredient in biologicals, devices and prescription medicines; and

There are no recorded adverse event reports for any related substances on the [Database of Adverse Events Notification \(DAEN\) - Medicines](#).

### ***International regulations***

#### *United Nations (UN)*

Cathinone and methcathinone are listed in Schedule I of the UN 1971 Convention on Psychotropic Substances. Amfepramone and pyrovalerone are in Schedule IV of that Convention, but other derivatives are not under international control. A few synthetic cathinones are controlled in some Member States under drug control or equivalent legislation, for example:

- Mephedrone (Belgium, Denmark, Germany, Estonia, Ireland, France, Italy, Lithuania, Romania, Sweden, Croatia and Norway);
- Methylone (Denmark, Ireland, Romania and Sweden);
- Butylone (Denmark, Ireland, Romania, Sweden and Norway);
- MDPV (Denmark, Ireland, Finland and Sweden); and
- Flephedrone (Denmark, Ireland and Romania).

Mephedrone is controlled under medicines legislation in Finland and the Netherlands. By Council Decision of 2 December 2010, 4-methylmethcathinone (mephedrone) was submitted to control measures in EU Member States (2010/759/EU).<sup>33</sup>

#### *United Kingdom (UK)*

Generic control in the UK covers a wide group of cathinone derivatives. In the UK, the 31 March 2010 report of the UK Advisory Council on the Misuse of Drugs – Consideration of the cathinones indicated that the harms associated with mephedrone and related cathinones were commensurate with the amphetamines and the substances in Class B. This UK report, defines cathinone derivatives generically as follows:

*Any compound (not being bupropion or a substance for the time being specified in paragraph 2.2) structurally derived from 2-amino-1-phenyl-1-propanone by modification in any of the following ways, that is to say,*

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<sup>33</sup> [The Europe Monitoring Centre for Drugs and Drug Addiction – Synthetic cathinones drug profile](#)

- i) by substitution in the phenyl ring to any extent with alkyl, alkoxy, alkylendioxy, haloalkyl or halide substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents;
- ii) by substitution at the 3-position with an alkyl substituent;
- iii) by substitution at the nitrogen atom with alkyl or dialkyl groups, or by inclusion of the nitrogen atom in a cyclic structure.

Present UK controls include:

- Cathinone (Class C), methcathinone (Class B), diethylpropion (Class C) and pyrovalerone (Class C) are controlled under the Misuse of Drugs Act 1971. However, other derivatives and analogues are not presently controlled (including mephedrone).
- Although the paragraph 1(c) of Part 1 (Schedule 2) of the *Misuse of Drugs Act 1971* offers some scope for the control of substances which are structurally related to the phenethylamine backbone, it is primarily concerned with ring-substituted amphetamine-like compounds. Specifically, no mention is made of the presence of any substituents (other than hydrogen) at the  $\beta$ -carbon of the phenethylamine backbone (cathinones all possess a  $\beta$ -ketone oxygen).
- Irrespective of whether controls for the cathinones are implemented under the *Misuse of Drugs Act 1971*, the rapidity and easy availability of mephedrone and other cathinones (including websites set up so that vendors that can deliver to individual addresses) does raise the question of whether other legislation and regulation should be available.

#### *United States of America (USA)*

In the USA, alpha-PVP (also known as alpha-pyrrolidinopentophenone) is reported by the [US DEA to be a synthetic cathinone and was temporarily placed in the US Schedule 1 of controlled drug substances in March 2017](#). After consideration of the relevant matter presented as a result of public comment, the scientific and medical evaluations and accompanying recommendations of the Department of Health and Human Services (HHS), and the DEA's consideration of its own eight-factor analysis, the DEA finds that these facts and all other relevant data constitute substantial evidence of potential for abuse of 4-MEC, 4-MePPP, alpha-PVP, butylone, pentadron, pentylone, 4-FMC, 3-FMC, naphyrone, and alpha-PBP. As such, the DEA is permanently scheduling them as controlled substances under the *Controlled Substances Act*.

See also the [DEA warning](#) in relation to synthetic cathinones.

#### *Canada*

Schedule I of the *Controlled Drugs and Substances Act*:

- Methylenedioxypropylone (MDPV), its salts, derivatives, isomers and analogues and salts of derivatives, isomers and analogues

**Table 1.5.1: Laws of Schedule I**

Offence	Punishment
Possession	Maximum 7 years imprisonment
Trafficking/possession for the purpose of	Maximum life imprisonment (mandatory minimum 1-year jail sentence for trafficking a Schedule I drug under 1 kg, 2 years if amount exceeds 2 kg)
Exportation/possession for the purpose of	Maximum life imprisonment

Production	Maximum life imprisonment
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Schedule III of the *Controlled Drugs and Substances Act*:

- Cathinone ((-)- $\alpha$ -aminopropiophenone) and its salts
- Methcathinone (2-Methylamino-1-phenyl-1-propanone) and its salts

**Table 1.5.2: Laws of Schedule III**

Offence	Punishment
Possession (requires a prescription to legally possess)	Maximum 3 years imprisonment
Trafficking/possession for the purpose of	Maximum 10 years imprisonment
Exportation/possession for the purpose of	Maximum 10 years imprisonment
Production	Maximum 10 years imprisonment

*New Zealand*

**Table 1.5.3: Medicine classifications in New Zealand**

Ingredient	Classification
Cathinone	Class B2 Controlled Drug
Methcathinone	Class B1 Controlled Drug
Monomethylpropion (synonym for methcathinone)	Class B1 Controlled Drug

### ***Substance summary***

Synthetic cathinones are chemically similar to cathinone, which comes from the khat plant (*Catha edulis*). Khat is a shrub grown in East Africa and southern Arabia, and people sometimes chew its leaves for their mild stimulant effects.

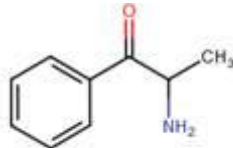
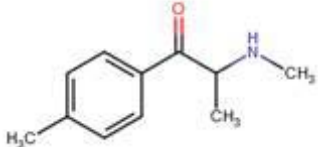
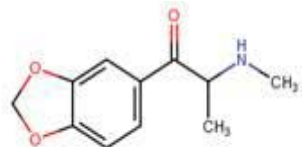
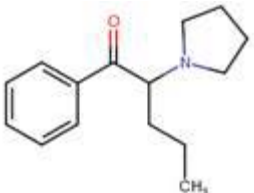
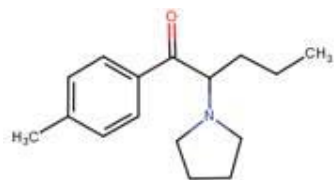
Synthetic cathinones are included in a group of drugs that concern public health officials called "new psychoactive substances" (NPS). NPS are unregulated psychoactive (mind-altering) substances that have become newly available on the market and are intended to copy the effects of illegal drugs. Some of these substances may have been around for years but have re-entered the market in altered chemical forms or due to renewed popularity.

The most well-known synthetic cathinone is mephedrone (4-MMC or meow meow), although there are several others, including methylone, alpha-PVP, methedrone, naphyrone, butylone and MDPV. These

substances reportedly produce similar effects to methamphetamine and MDMA (ecstasy).<sup>34</sup> Synthetic cathinones have only been used as street drugs since the 2000s.<sup>35</sup>

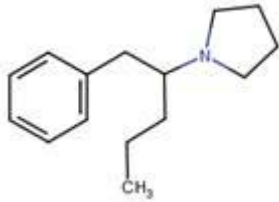
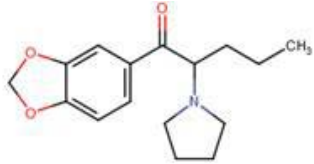
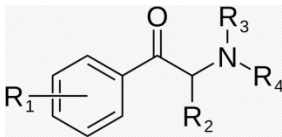
Until recently, these drugs were available under the guise of 'research chemicals' or 'plant food', either online or in shops which sell legal highs.

**Table 1.5.4: Chemical properties of cathinone and some synthetic cathinones**

Chemical	CAS number	IUPAC and/or common and/or other names	Molecular structure and weight	Structure
Cathinone	42542-10-9	1-(1,3-benzodioxol-5-yl)- <i>N</i> -methylpropan-2-amine (IUPAC);  Mandy, MDMA, Molly, ecstasy;	C <sub>11</sub> H <sub>15</sub> NO <sub>2</sub>  193.2 g/mol	
Mephedrone (4-methylmethcathinone)	1189805-46-6	2-(methylamino)-1-(4-methylphenyl)propan-1-one (IUPAC);  M-CAT, HSB 7979, Meow Meow, Bounce, Bubbles;	C <sub>11</sub> H <sub>15</sub> NO  177.2 g/mol	
Methylone	186028-79-5	1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one (IUPAC);  BK-MDMA, HSB 7997, M1;	C <sub>11</sub> H <sub>13</sub> NO <sub>3</sub>  207.2 g/mol	
alpha-PVP	14530-33-7	1-phenyl-2-pyrrolidin-1-ylpentan-1-one (IUPAC);  Flakka, Gravel, O-2387, beta-Keto-prolintane;	C <sub>15</sub> H <sub>21</sub> NO  231.3 g/mol	
Pyrovalerone	3563-49-3	1-(4-methylphenyl)-2-pyrrolidin-1-ylpentan-1-one (IUPAC);	C <sub>16</sub> H <sub>23</sub> NO  245.4	

<sup>34</sup> Fantegrossi, W.E., *et al.*, *In vivo* Effects of Abused 'Bath Salt' Constituent 3,4-methylenedioxypyrovalerone (MDPV) in Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity. *Neuropsychopharmacology*, 2013. 29: p. 563-573.

<sup>35</sup> Winstock, A.R., *et al.*, Mephedrone, new kid for the chop? *Addiction*, 2011. 106(1): p. 154-61.

Prolintane	493-92-5	1-(1-phenylpentan-2-yl)pyrrolidine (IUPAC); Catovit;	C <sub>15</sub> H <sub>23</sub> N 217.4 g/mol	
3,4-methylenedioxypropylamphetamine (MDPV)	687603-66-3	1-(1,3-benzodioxol-5-yl)-2-pyrrolidin-1-ylpentan-1-one (IUPAC); MDPV, MDPK;	C <sub>16</sub> H <sub>21</sub> NO <sub>3</sub> 275.3 g/mol	
General chemical structure of a cathinone derivative showing substitution patterns				

Cathinones act as central nervous system stimulants, although the potencies of the cathinones are generally lower than their amphetamine congeners. This may be due to the increased polarity conferred on a cathinone by the presence of a  $\beta$ -keto group reducing their ability to cross the blood-brain barrier.

Cathinone derivatives are the  $\beta$ -keto ( $\beta$ k) analogues of a corresponding phenethylamine. Synthetic variants of cathinone can be much stronger than the natural product and, in some cases, very dangerous.<sup>36</sup>

Cathinone is structurally very similar to amphetamine (1-phenylpropan-2-amine), differing only in the functionality present at the  $\beta$ -carbon. Cathinone possesses a ketone oxygen at the  $\beta$ -carbon; cathinone can therefore be considered as the ' $\beta$ -keto analogue' of amphetamine. The molecular architecture of 2-amino-1-phenyl propanone (cathinone) can be altered to produce a series of different compounds which are closely structurally related to cathinone. Together these are known as the 'cathinones', 'synthetic cathinones' or 'cathinone derivatives'.

The basic cathinone structure can be altered in a number of predictable ways, such as the inclusion of additional functionality to the aromatic ring (ring substitution, R<sub>1</sub>), N-alkylation (or inclusion of the nitrogen atom in a ring structure, R<sub>3</sub> and R<sub>4</sub>), and variation of the (typically alkyl)  $\alpha$ -carbon substituent (R<sub>2</sub>). Multiple modifications may be present in a single derivative. Cathinones are all usually N-alkylated (or the nitrogen is incorporated into a ring structure, typically pyrrolidine) and many also bear ring substituents.

### **Pre-meeting public submissions**

Three (3) public submissions were received that opposed the proposal for for alpha-PVP and related substances (cathinones and methylone), instead suggesting that a Schedule 9 entry may be more appropriate. The main points opposed to a Schedule 4 entry and in support of a Schedule 9 entry were:

- Methylone (MDMC) and alpha-pyrrolidinovalerophenone (alpha-PVP) are synthetic psychostimulants associated with overdoses, suicides and illicit use.
- The poisons information centres and clinical toxicology units around Australia continue to be contacted for advice on poisonings from these agents. Features of these poisonings include

<sup>36</sup> Baumann MH. Awash in a sea of 'bath salts': implications for biomedical research and public health. *Addiction*. 2014;109(10):1577-1579.

agitation, tachycardia, hypertension and in severe cases delirium, aggressive behaviour, hallucinations, hyperthermia, cardiac dysrhythmias and seizures. Deaths have occurred due to alpha-PVP toxicity.

- Cathinones, MDMC and alpha-PVP have no currently established therapeutic value and have demonstrated high risks of dependency, abuse, misuse and illicit use; and possess a significant toxicity profile which fits the criteria for inclusion in Schedule 9. Schedule 4 and Appendix D are not appropriate.
- Cathinones are illegal in many other countries such as the United States of America, the United Kingdom, Sweden and New Zealand.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that new Schedule 9 entries be created for alpha-PVP and methyldone in the Poisons Standard, and the current Schedule 9 cathinone entry be amended as follows:

#### **Schedule 9 – New Entry**

**ALPHA-PYRROLIDINOVALEROPHENONE \*(ALPHA-PVP).**

#### **Schedule 9 – New Entry**

**METHYLONE \*(MDMC).**

#### **Schedule 9 – Amend Entry**

**CATHINONES except when separately specified in these Schedules.**

#### **Index – Amend Entry**

#### **CATHINONES**

**cross reference: SYNTHETIC CATHINONES**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the advice comprised the following:

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

- Risks: These classes of substances collectively are associated with considerable toxic effects as evidenced by reports of mortality and poisons data. Risks of consumption by humans are significant.
- Benefits: There was no benefit of use found.

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

- No established therapeutic purpose or use (except cathinone-structure medicines are already included in Schedule 4). There is evidence these substances are used as recreational drugs worldwide, including in Australia, with consequent significant public health harm.
- Readily available in internet and retail stores.

*c) the toxicity of a substance:*



- Significant stimulant and psychoactive effects. Human use has resulted in death.
- Toxic effects include agitation, tachycardia, hypertension, delirium, aggression, hyperthermia, cardiac arrhythmias and seizures. There has been reported mortality in Australia and internationally. With mephedrone in particular, there are deaths reported in England, Scotland, Wales and Sweden.

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

- N/A – generally ‘white powders’.
- Doses of MDPV reported as 5 mg or less, mephedrone as 200 mg or more with repeated redosing up to 1-2 g per ‘session’.

e) the potential for abuse of a substance:

- Animal studies indicate many cathinone substances have addiction potential.

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

- Alpha-PVP, methylone and some synthetic cathinones are already controlled through misuse of drugs legislation across Australia.
- Increasingly, there are similar controls internationally.

### ***Delegate’s considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS 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 create a new Schedule 9 entries for alpha-pyrrolidinovalerophenone and methylone, as well as amend the Schedule 9 entry for cathinone. The proposed Schedule entries are:

#### **Schedule 9 – New Entry**

ALPHA-PYRROLIDINOVALEROPHENONE \*(ALPHA-PVP).

#### **Schedule 9 – New Entry**

METHYLONE \*(MDMC).

#### **Schedule 9 – Amend Entry**

CATHINONES **except** when separately specified in these Schedules.

#### **Index – Amend Entry**

#### **CATHINONES**

cross reference: SYNTHETIC CATHINONES

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- Risks: These classes of substances collectively are associated with considerable toxic effects as evidenced by reports of mortality and poisons data. Risks of consumption by humans are significant.
- Benefits: There was no benefit of use found.

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

- No established therapeutic purpose or use (except cathinone-structure medicines are already included in Schedule 4). There is evidence these substances are used as recreational drugs worldwide, including in Australia, with consequent significant public health harm.
- Readily available in internet and retail stores.

c) *the toxicity of a substance:*

- Significant stimulant and psychoactive effects. Human use has resulted in death.
- Toxic effects include agitation, tachycardia, hypertension, delirium, aggression, hyperthermia, cardiac arrhythmias and seizures. There has been reported mortality in Australia and internationally. With mephedrone in particular, there are deaths reported in England, Scotland, Wales and Sweden.

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

- N/A – generally ‘white powders’.
- Doses of MDPV reported as 5 mg or less, mephedrone as 200 mg or more with repeated redosing up to 1-2 g per ‘session’.

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

- Animal studies indicate many cathinone substances have addiction potential.

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

- Alpha-PVP, methylone and some synthetic cathinones are already controlled through misuse of drugs legislation across Australia.
- Increasingly, there are similar controls internationally.

## **1.6 Ibuprofen**

### ***Referred scheduling proposal***

An application was submitted to amend the Schedule 2 and Schedule 3 entries in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### ***Scheduling application***

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

## Schedule 2 – Amend Entry

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or
- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than ~~100~~ 30 dosage units **except when:**
  - ~~i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);~~
  - ~~ii) packed in blister or strip packaging or in a container with a child-resistant closure;~~
  - ~~iii) in a primary pack containing not more than 25 dosage units;~~
  - ~~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 phenylephrine.~~

## Schedule 3 – Amend Entry

IBUPROFEN **for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen and not labelled for the treatment of children under 12 years of age:**

- a) in divided preparations each containing 200 mg or less of ibuprofen in a primary pack containing not more than 100 dosage units
- b) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

**except** when included in ~~or expressly excluded from~~ Schedule 2.

On 29 June 2017, the delegate decided to amend the Schedule 3 entry to include a modified release dosage form of ibuprofen. As a result, the secretariat has amended the proposed entry for consistency with the delegate's decision, which came into effect on 1 October 2017:

## Schedule 3 – Amend Entry

IBUPROFEN:

- a) **in divided preparations, each containing 200 mg or less of ibuprofen in a primary pack containing not more than 100 dosage units, when labelled:**
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and**
  - ii) not for the treatment of children under 12 years of age; or**
- a)b) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age; or
- b)c) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:

i) with a recommended daily dose of 1200 mg or less of ibuprofen; and

ii) not for the treatment of children under 12 years of age;

**except** when included in or ~~expressly excluded from~~ Schedule 2.

The applicant's reasons for the request are:

- Over-the-counter (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used pharmacological agents worldwide to treat mild to moderate pain. Ibuprofen is the most commonly used NSAID.
- Ibuprofen is currently the only oral NSAID exempt from scheduling that can be sold in general retail with no access to professional advice regarding appropriate use. The current maximum pack size of 100 dosage units is also significantly larger than other type of oral NSAID listed in Schedule 2.
- Several recent major international studies have highlighted the increased risk of heart failure associated with NSAIDs at OTC doses. Additionally, clearer warnings regarding the use of NSAIDs during preconception and pregnancy have been adopted as per recommendation by the Therapeutic Goods Administration (TGA). Noted in the 2014 TGA safety review of NSAIDs:

*'NSAIDs are among the most commonly used pharmacological agents worldwide due to their efficacy as non-addictive analgesics and their anti-inflammatory properties. Hence, even a small absolute risk of serious cardiovascular effects associated with these drugs could produce a significant health burden in a given population.'*

- The proposed amendments to the Schedule 2 listing for ibuprofen are a prudent response to the recent and mounting evidence regarding the risks associated with NSAIDs. The proposed changes will mitigate these risks and facilitate access to these medicines so that patients will gain optimal health outcomes.
- Low levels of consumer health literacy regarding the safe maximum daily dose of ibuprofen warrants tighter controls on the supply of ibuprofen. This applies particularly to outlets where there are no restrictions on the number of packs that can be purchased by consumers and no access to professional advice or administration under professional health care supervision and guidance.
- This application should also be viewed in the context of the deletion of Schedule 2 and Schedule 3 entries for codeine, taking effect on 1 February 2018. From this date, many consumers who were previously taking Schedule 3 codeine medicines (specifically combination analgesics containing codeine) will likely seek alternatives that may include ibuprofen either as a single active ingredient or in combination with paracetamol. This will likely lead to increased use of ibuprofen, which will further exacerbate these risks.
- Providing consumer access to information via hand-outs or labelling is not sufficient to address the concerns raised. Facilitating access to professional advice for the prescribing and supply of medicines is the best way to maintain safe and cost-effective access to medicines. Consumers need advice on the correct and proper way to use medicines. This is best achieved with supply from a pharmacist through a community pharmacy and when necessary, referral to a general practitioner or appropriate health care professional.
- Large packs of ibuprofen for longer term use should only be available as a Schedule 3 medicine. The mandatory intervention of a pharmacist will determine whether a larger pack size is therapeutically appropriate and will facilitate discussions regarding pain management. Recommendations on potentially more suitable medicines and referral to other health practitioners can be made as required.

### ***Current scheduling status***

Ibuprofen is currently listed in Schedules 2, 3 and 4 and Appendix F, Part 3 and Appendix H of the Poisons Standard as follows:

## Schedule 2

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or
- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
  - i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);
  - ii) packed in blister or strip packaging or in a container with a child-resistant closure;
  - iii) in a primary pack containing not more than 25 dosage units;
  - 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 phenylephrine.

## Schedule 3

IBUPROFEN:

- a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age; or
- b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age,

**except** when included in or expressly excluded from Schedule 2.

## Schedule 4

IBUPROFEN **except**:

- a) when included in or expressly excluded from Schedule 2 or 3; or
- b) in preparations for dermal use.

## Appendix F, Part 3

Warning Statements: 101, 104

## Appendix H

IBUPROFEN.

## ***Scheduling history***

In November 1985, the National Health and Medical Research Council (NHMRC) considered a request to amend the scheduling of ibuprofen from Schedule 4 to Schedule 2 as ibuprofen was not scheduled in Victoria. It was agreed there were anaphylactic problems with people sensitive to aspirin. It was decided not to alter the scheduling.

In November 1987 the NHMRC considered a request to move ibuprofen from Schedule 4 to Schedule 2 with pack size restrictions. The committee was of the opinion that there was a place for ibuprofen outside Schedule 4. Recommendation for a new Schedule 3 entry with pack size restrictions of less than 50 tablets or capsules (200 mg).

In May 1995, the NDPSC considered proposal for a new Schedule 2 entry for ibuprofen and agreed to a new entry. Schedule 4 entry amended. New Schedule 2 for ibuprofen in divided preparations for oral use containing 200mg or less with a recommended dose of 1200mg or less.

In November 1998, the NDPSC considered an application for ibuprofen liquid suspension 100 mg/5 mL to be rescheduled from Schedule 4 to Schedule 2. Overall, the committee considered that a Schedule 3 classification was more appropriate for this formulation, and agreed that the Poisons Standard be amended accordingly. The committee agreed that a maximum daily dose should be stipulated, but because the proposed pack size was 200 mL (maximum of 4 g ibuprofen) a restriction on total content was not required for this classification. A new entry for Schedule 3 was agreed in undivided preparations for oral use when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen.

In May 2000, the NDPSC considered a proposal to amend the Schedule 2 entry for ibuprofen to include oral liquid preparations containing more than 20 mg/1 mL. The committee considered the safety profile of ibuprofen and that Schedule 2 is appropriate when used in analgesic dose for minor and temporary ailments for short periods. The committee was seeking consistency with divided dose formulations.

In June 2003, the NDPSC considered a proposal to exempt ibuprofen from scheduling in divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 24 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen. The NDPSC decided to exempt ibuprofen from scheduling as requested, but with an amended maximum pack size (25 dosage units) and additional restrictions as follows: ibuprofen as the only therapeutically active constituent other than an effervescent agent; and requirements for label warnings (consistent with Appendix F warnings for Schedule 2 ibuprofen). The minutes note that the NDPSC had agreed that the schedule wording should be comparable with that of the current aspirin and paracetamol entries.

In October 2003, following consideration of further public submissions, the NDPSC made some amendments to the label warning statements required for ibuprofen when exempted from scheduling, in particular, by adding warnings not to use the product unless advised by a doctor in children ages 6 years or less, or by people aged 65 years or over.

The NDPSC subsequently made some editorial amendments to the Schedule 2 exemption in June 2004 and February 2005.

In August 2010 the NDPSC considered the scheduling of paracetamol in combination with ibuprofen in June 2010. At that time, divided dose combinations containing up to 200 mg ibuprofen + 500 mg paracetamol were included in Schedule 2 (when labelled with a maximum daily dose of 1200 mg ibuprofen, and in packs of up to 100 dosage units). The NDPSC recommended, and the delegate confirmed, that the scheduling of ibuprofen and paracetamol that was current at that time remained appropriate.

In June 2011 the ACMS considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a



combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination.

The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice.

In February 2013 the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

In June 2012, the ACMS considered a submission to reschedule ibuprofen from Schedule 2 to unscheduled when in divided preparations containing 200 mg or less of ibuprofen in fixed dose combination with 5 mg or less of phenylephrine, in packs containing not more than 25 tablets. ACMS recommended to the delegate that ibuprofen in combination with phenylephrine should be exempt from scheduling, as requested. The delegate decided to also restrict the scheduling exemption to use for the treatment of adults and children aged 12 years of age and over.

In November 2015, the ACMS considered a submission to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS recommended that paracetamol should be included in Schedule 2 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 pack of not more than 3 day supply. The delegate agreed with the ACMS and made an interim decision based on the ACMS advice. After deferring their final decision to give consideration to a late submission received during the interim decision consultation period, the delegate decided to vary their decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considers it is more appropriate to limit the Schedule 2 part a) entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive.

In March 2017, the ACMS considered a proposal to amend the Schedule 3 entry for ibuprofen to include a modified release dosage form of 600 mg of ibuprofen per dosage unit in packs of 32 or less dosage units. ACMS recommended that the Schedule 3 entry should be amended as suggested, allowing consumers greater access to a product for pain relief that is longer-lasting than other products currently available. The delegate's final decision was to amend the Schedule 3 entry for ibuprofen to include the modified release dosage form, with an implementation date of 1 October 2017.

### ***Australian regulatory information***

The Australian Register of Therapeutic Goods (ARTG) has 229 entries for products containing ibuprofen. They are approved for treatment of infants, children and adults and come in multiple dosage strengths and forms.

Combination products available include ibuprofen with codeine, ibuprofen with paracetamol and ibuprofen with pseudoephedrine. The ARTG also included entries for ibuprofen lysine 324 mg tablets and capsules and ibuprofen sodium dihydrate 256 mg tablets and capsules.



In the last 30 years there have been 1222 reported cases of adverse events related to ibuprofen in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 813 cases with a single suspected medicine and 35 cases where death was a reported outcome.

According to the [TGA Ingredient Database](#), ibuprofen, ibuprofen lysine and ibuprofen sodium dihydrate are available for use as an:

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

### **International regulations**

#### *Canada*

Health Canada regulates ibuprofen in strengths of 200 mg, 300 mg and 400 mg as over-the-counter medicines.

#### *New Zealand (NZ)*

Medsafe NZ regulates ibuprofen in solid dose forms containing not more than 200 mg in packs of more than 25 and less than 100 tablets as Pharmacy Only.

#### *United States of America (USA)*

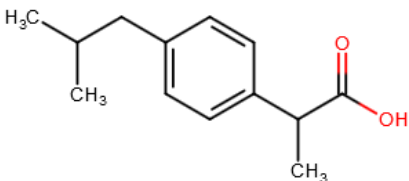
The USA Food and Drug Administration regulate ibuprofen in varying dose forms as an over-the-counter medicine.

#### *European Union*

The European Medicines Authority regulates ibuprofen and dexibuprofen (the dextrorotatory enantiomer of ibuprofen) in varying doses and formulations and these are available on prescription as well as over the counter.

### **Substance summary**

**Table 1.6.1: Chemical information of ibuprofen**

Property	Ibuprofen
CAS name	Ibuprofen
CAS number	15687-27-1
IUPAC and/or common and/or other names	2-[4-(2-methylpropyl)phenyl]propanoic acid (IUPAC); Ibuprofen (INN);
Chemical structure	
Molecular formula	C <sub>13</sub> H <sub>18</sub> O <sub>2</sub>

Molecular weight	206.3 g/mol
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Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an analgesic, antipyretic, and anti-inflammatory. It decreases synthesis of pain and inflammation, promoting prostaglandins via non-selective inhibition of both cyclo-oxygenase 1 and 2 (COX-1 and COX-2) enzymes.

Ibuprofen is a white or almost white, crystalline powder or colourless crystals. It is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Numerous oral non-prescription ibuprofen formulations are available in Australia with various dosage forms, strengths and combinations. These 'immediate release' (IR) non-prescription formulations are indicated for the management of mild to moderate pain and inflammation, including reducing fever, and for the treatment of headache including migraine, period pain, dental pain, musculoskeletal and joint pain and post-operative pain.

Australian therapeutic guidelines recommends that the non-prescription ibuprofen oral dose in people aged more than 12 years of age is 200-400 mg every 4 to 6 hours as needed, with a maximum daily dose of 1200 mg.

Toxic effects are unlikely at doses below 100 mg/kg, but can be severe above 400 mg/kg. Risks noted include increased risk of cardiac arrest, risk of spontaneous abortion, risk of gastrointestinal side effects (including bleeding), as well as renal function changes. Additionally, NSAIDs such as ibuprofen may not be suitable for people with stomach problems such as ulcers or bleeding, people with heart or kidney problems or people with high blood pressure.

### ***Pre-meeting public submissions***

Seventeen (17) submissions were received, three (3) in support and fourteen (14) opposed.

#### *Main points in support:*

- Rescheduling of codeine is likely to increase the use of ibuprofen.
- Guidance and counselling from a pharmacist should be readily available to avoid medication misuse, and to confirm baseline risk factors, comorbidities and medication use to provide individualised treatment.
- Co-administration of ibuprofen with combination tablets of angiotensin-converting-enzyme inhibitor (ACE inhibitor) or Angiotensin II Receptor Blockers (ARBs) with a diuretic for treating hypertension can increase the potential for renal adverse medication events.
- Co-administration of NSAIDs with antithrombotic drugs could result in a major bleeding event.
- Rescheduling ibuprofen would reduce the incidence of self-selection of ibuprofen to treat pain or muscular inflammation.
- Two comprehensive reviews of NSAIDs conducted by the TGA in recent years acknowledged the cardiovascular, hepatotoxicity and pregnancy risks associated with these medicines. Thus it is appropriate that access to these medicines is restricted further to ensure appropriate review by a pharmacist.
- Ibuprofen has a good safety profile for use at over-the-counter doses and short term therapy.
- NSAIDs are potent substances particularly for individuals with risk factors such as asthma, hypertension, renal impairment or heart failure. The wide availability of NSAIDs both OTC and prescription ultimately pose a risk to consumers who may inadvertently take different NSAIDs concurrently or continue therapy for a longer period than clinically necessary.

- At least 50% of all patients, and at least 60% of patients diagnosed with a musculoskeletal disorder had at least one NSAID-relevant coexisting medical condition as identified in a recent study. The frequency of NSAID-relevant coexisting medical conditions also increased with age.<sup>37</sup>
- Some consumers are known to increase their OTC dose when analgesia is suboptimal.
- Ibuprofen should be considered in the context of scheduling of similar substances such as naproxen given the similar safety profiles.

*Main points opposed:*

- A previous proposal to reschedule ibuprofen to restrict sale to pharmacies was considered in 2014/15 and was rejected on the grounds that there was insufficient evidence. There have been no new safety alerts or concerns raised since that time to warrant a further review or a change in the scheduling of ibuprofen.
- The TGA (in 2014 and 2016) and the European Medicines Agency (EMA) (in 2015) have both recently conducted safety reviews of NSAIDs, including ibuprofen; these reviews have stated that there is minimal cardiovascular risk associated with ibuprofen when used at recommended OTC doses and duration
- The reviews did not recommend that any changes to access are warranted and proposed new labelling warning statements to improve consumer awareness of risks associated with use by people who have risk factors or use for prolonged periods of time
- Since the reviews were published there has been no evidence of any significant public health concern that could have altered the risk vs benefit profile of ibuprofen, to warrant a departure from the current scheduling arrangements.
- In many international markets, ibuprofen is available through general retail stores. Ibuprofen scheduling in Australia is in line with all major international countries, including the UK, Canada, the USA and New Zealand.
- Ibuprofen (200 mg in small packs and up to 25 dosage units) has been available through retail stores as an unscheduled medicine since 2003 and as a pharmacy medicine (Schedule 2) for over 2 decades. There is no apparent reason why ibuprofen in small pack sizes should be restricted in a way that sees consumers purchasing from a pharmacy instead of a general retail store.
- Ibuprofen is currently available from pharmacies in larger pack sizes, allowing consumers to obtain advice when required.
- Up-scheduling ibuprofen will not provide any significant additional health care professional supervision, with interaction typically provided by a pharmacy assistant, and will only result in reduced access to general pain relief to consumers.
- Rescheduling would reduce the consumer's ability to self-select pain medication when pharmacies are closed, especially in rural/remote Australia.
- Restricting the sale of ibuprofen to pharmacies only would deny Australian consumers appropriate and timely access to a safe and effective analgesic, thereby limiting their ability to effectively treat or manage sudden symptoms or minor ailments. As such, this would have a negative impact on public health.
- Ibuprofen has an excellent, well known safety profile and the use of labelling and safety warnings facilitates appropriate use by the consumer.

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<sup>37</sup> [Bloom L, Blacketer M, Boyle K et al. Aging and the frequency of NSAID-relevant coexisting medical conditions in the primary care setting. Innovation in Aging 2017;1\(suppl 1\):875.](#)

- Access to ibuprofen is currently similar to that of other products used for short term pain relief such as paracetamol and aspirin.
- Ibuprofen continues to demonstrate a favourable benefit versus risk profile.
- Ibuprofen has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low. The consequences of misuse of paracetamol are substantially worse than with ibuprofen. There is a low incidence of adverse events relating to the consumption of ibuprofen given the large number of dosage units that are sold unscheduled in Australia.
- The proposed changes to the scheduling will have a significant impact on consumer choice and convenience, reduce competition and increase cost to consumers.
- Limiting options and accessibility will not deliver any health benefits to the community. It may result in possible public health consequences such as those arising from increased consumption of paracetamol.
- Education of at risk patients and improved product labelling would be more effective measures with a greater impact than reduced convenience and impeded access.
- For consumers, OTC medicine labels provide the single most important source of information. Australian medicines that contain ibuprofen must be labelled in accordance with the Required Advisory Statements for Medicine Labelling (RASML), which contains detailed mandatory warning statements in language that consumers are able to understand and act upon.
- Any increase in regulation should be based on sound evidence that (i) the concerns are based on accurate evidence and (ii) that scheduling changes are the only mechanism for addressing these concerns.
- Small packs of ibuprofen that are currently exempt (i.e. 25 dosage units / approximately 4 days' supply) can be appropriately selected and used by the reasonable consumer with acceptable safety.
- A thorough and transparent public examination of the evidence behind this scheduling proposal is required and any regulatory decisions should be consistent with the principles of best practice regulation.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that the current Schedule 2 and Schedule 3 entries for ibuprofen remain appropriate.

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

The reasons for the advice comprised the following:

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

- Risks:
  - Increased incidence of NSAID (ibuprofen) cardiovascular (CV) effects especially (but not exclusively) in people at risk at high doses and longer duration than OTC doses.
  - There are no new safety concerns. The evidence of potential CV risk associated with OTC doses of ibuprofen is not substantiated (Bally M *et al.*, BMJ 2017).

- Benefits: 24 hour availability of 24 pack sizes as exempt for acute pain.
- b) the purposes for which a substance is to be used and the extent of use of a substance:
  - OTC Indication is for acute pain (1200 mg/day for short term of not more than 4 days).
- c) the toxicity of a substance:
  - Cardiovascular disease and other complications of NSAID use (gastrointestinal, blood pressure, renal impairment); confusion in elderly.
  - Covered by RASML statement.
- d) the dosage, formulation, labelling, packaging and presentation of a substance:
  - Covered by RASML statement.
- e) the potential for abuse of a substance:
  - Ibuprofen is non-addictive.
  - Minimal risk of misuse or abuse.
- f) any other matters that the Secretary considers necessary to protect public health
  - Ibuprofen (200 mg in small packs and up to 25 dosage units) has been available through retail stores as an unscheduled medicine since 2003 and as a Pharmacy Medicine (Schedule 2) for over 2 decades.
  - No evidence provided of excessive use, purchasing or harm through general sale or Schedule 2 availability.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS 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 that the current Schedule 2 and Schedule 3 entries for ibuprofen remain appropriate.

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

The reasons for the recommendation comprised the following:

- a) the risks and benefits of the use of a substance:
  - The October 2014 TGA 'Review of cardiovascular safety of non-steroidal anti-inflammatory drugs' stated:

*Based on the current evidence, there are no major changes required to the availability and warnings on labels for over-the-counter (OTC) diclofenac, ibuprofen and naproxen. These drugs provide effective pain relief when used according to the label at recommended doses for short durations.*

- EMA advice in May 2015 following a review was:

*No increase in cardiovascular risk is seen with ibuprofen at doses of up to 1,200 mg per day, which is the highest dose generally used for over-the-counter (OTC) preparations taken by mouth in the European Union (EU).*

- There are no new safety concerns. The evidence of potential cardiovascular (CV) risk associated with OTC doses of ibuprofen is not substantiated (Bally M *et al.*, BMJ 2017).
- Risks: increased incidence of NSAID (ibuprofen) CV effects are especially (but not exclusively) seen in people at risk, at high doses and at longer duration, rather than OTC doses.
- Benefits:
  - 24 hour availability of 24 pack sizes as exempt for acute pain.
  - Ibuprofen has a good safety profile for use at over-the-counter doses and short term therapy.

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

- Indication is for acute pain (1200 mg/day for short term of not more than 4 days).

*c) the toxicity of a substance:*

- Although there are cardiovascular disease and other complications of NSAID use (gastrointestinal, blood pressure, renal impairment) and confusion in the elderly these are well covered in the labelling as per the RASML statement.
- Ibuprofen has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low.

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

- RASML statement and hence the labelling mitigate any risk.
- Ibuprofen scheduling in Australia is in line with major international countries including the UK, Canada, the USA and New Zealand.
- There is 24 hour availability of exempt pack sizes for acute pain as well as easy accessibility in rural/remote areas.

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

- Minimal risk of misuse or abuse.

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

- No evidence provided of excessive use, purchasing or harm through general sale or Schedule 2 availability.
- Ibuprofen scheduling in Australia is in line with major international countries including the UK, Canada, the USA and New Zealand.

## 1.7 Melanotan II

### *Referred scheduling proposal*

An application was submitted to create a new entry in Schedule 10 for melanotan II in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

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

#### **Schedule 10 – New Entry**

**MELANOTAN II for cosmetic or therapeutic use.**

#### **Index – New Entry**

#### **MELANOTAN II**

**cross reference  $\alpha$ -MELANOCYTE STIMULATING HORMONE**

#### **Schedule 10**

The applicant's reasons for the request are:

- Melanotan II is a synthetic analogue of the  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH).  $\alpha$ -MSH is a melanocortin I receptor agonist which has a role in human pigmentation by stimulating production of eumelanin. Melanotan II was originally developed as a treatment for sexual dysfunction. However, the proposal was abandoned when development of the metabolite bremelanotide was established.
- Melanotan II is being abused as an injectable subcutaneous lifestyle drug for the purposes of sunless tanning, appetite suppression and sexual stimulation.
- Melanotan II has reported toxicity effects from therapeutic and overdose exposures including: renal dysfunction, rhabdomyolysis, sympathomimetic overdrive, change in size and pigmentation of pre-existing moles, rapid increase in the number of new moles associated with causing melanomas, posterior reversible encephalopathy syndrome, refractory priapism, stretching and yawning syndrome, shortness of breath, chest pain, abdominal cramping and pain, dizziness and lethargy. XXXXXX alone has received 28 calls about melanotan II since 2006.
- The therapeutic dose is considered to be 0.01 mg/kg. However, reports from XXXXXX show that overdose appears to be relatively common, and hospitalisation is usually required.
- Quality, safety and efficacy data for this product has not been established. There is also an unknown infection risk and case reports have detailed positive testing on these products for microbial contaminants.
- Post reconstitution, vials are marketed for multiple uses for up to a few weeks, which could compound the infection risk and additionally, raises the issue of stability.
- The unregulated nature of these products may falsely lead consumers to believe that these products are safe, in the absence of any detailed risk analysis.
- There is no clinical safety and efficacy data and the side effects and toxicity profile greatly outweigh any benefits of use. Restricting the sale, possession or supply of this substance is in the public health's best interests.

### *Current scheduling status and relevant scheduling history*

Melanotan II is not specifically scheduled. Therefore a scheduling history is not available.



Related substances listed in the [Poisons Standard](#)

#### **Schedule 4**

AFAMELANOTIDE.<sup>38</sup>

ADRENOCORTICAL HORMONES **except** when separately specified in these Schedules.

CORTICOTROPHIN.

*Scheduling history of related substances:*

#### **Afamelanotide**

In December 2010, the delegate made a delegate only decision to include afamelanotide (also known as melanotan I) with a cross-reference to melanocyte stimulating hormone (MSH) for inclusion into the current Poisons Standard. It was noted that afamelanotide should not be confused with a similar substance commonly known as Melanotan-II, which is a cyclic lactam synthetic analogue of  $\alpha$ -MSH. It was noted that melanotan-II was under investigation for treating sexual dysfunction, although this has been abandoned due to side effects associated with the immune and cardiovascular systems. Its metabolite, bremelanotide, is under investigation for treating haemorrhagic shock.

#### **Adreno-corticotrophic hormone**

In January 1955, adreno-corticotrophic hormone (ACTH) was included in the very first Poisons Schedules. It was included in Schedule 4, Part A, which is equivalent to the current Schedule 4 of the Poisons Standard. Provisions for a repeated script must be authorised by an authorised prescriber, including general practitioners, veterinarian or dentist (if required for the purposes of the dental profession or are permitted to be prescribed by a dentist).

#### **Corticotrophin**

In May 1956, corticotrophin and other pituitary hormones for parenteral use in humans were included in Schedule 4 of the Draft Uniform Poisons Schedules.

#### **Australian regulatory information**

Melanotan II is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

#### **International regulations**

##### *New Zealand (NZ)*

Medsafe NZ classifies '*melanocyte stimulating compounds*' as prescription medicines.

##### *United States of America (USA)*

According to the USA Food and Drugs Administration (FDA) website, melanotan I, melanotan II and bremelanotide are unapproved injectable drugs in the USA.

In September 2007, the FDA issued a public notice advising consumers to stop using melanotan II as it was an unapproved drug with no safety or efficacy data for the advertised indications. Furthermore,

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<sup>38</sup> Also known as melanotan I; cross referenced to MELANOCYTE STIMULATING HORMONE in the index

the FDA issues a warning notice to a company owner that was illegally selling and marketing the product via a website. This led to subsequent indictment.

### European Union (EU)

The European Medicines Agency granted orphan designation to  $\alpha$ -melanocyte stimulating hormone for the treatment of erythropoietic porphyria.

Multiple European governing authorities including Danish Medicines Agency, Norwegian Medicines Agency, Swedish Medical Products Agency, United Kingdom Medicines and Healthcare products Regulatory agency have issued warnings on the sale and use of melanotan products.

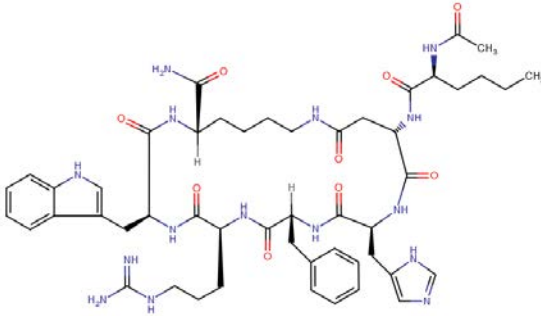
### United Kingdom (UK)

In November 2008, the UK Medicines and Healthcare products Regulatory Agency (MHRA) warned the public against melanotan use stating it was an unlicensed medicine that may not be safe. As such, it is illegal to market or supply this product in the UK due to its unlicensed nature. Additionally the MHRA warned 18 companies about selling or advertising the product and closed down 72 websites involving melanotan. By 2013, the MHRA had received 18 reports of 74 separate reactions to the products and reactions have involved stomach and heart problems, as well as blood and eye disorders.

In February 2009, the Irish Medical Board (IMB) indicated that they had detected the presence of microbial contamination in the water vial supplied with melanotan which poses a risk of serious infection. Further the IMB stated that this product is not authorised for use in the EU due to no guarantees as to quality, safety or efficacy.

### Substance summary

**Table 1.7.1: Chemical information of melanotan II**

Property	Melanotan II
CAS name	Melanotan II acetate salt
CAS number	121062-08-6
IUPAC and/or common and/or other names	(3 <i>S</i> ,6 <i>S</i> ,9 <i>R</i> ,12 <i>S</i> ,15 <i>S</i> ,23 <i>S</i> )-15-[[[(2 <i>S</i> )-2-acetamidohexanoyl]amino]-9-benzyl-6-[3-(diaminomethylideneamino)propyl]-12-(1 <i>H</i> -imidazol-5-ylmethyl)-3-(1 <i>H</i> -indol-3-ylmethyl)-2,5,8,11,14,17-hexaoxo-1,4,7,10,13,18-hexazacyclotricosane-23-carboxamide (IUPAC);
Chemical structure	
Molecular formula	C <sub>50</sub> H <sub>69</sub> N <sub>15</sub> O <sub>9</sub>
Molecular weight	1024.2 g/mol

Melanotans include melanotan I (afamelanotide) and melanotan II. Both melanotan I and II are widely abused to obtain a cosmetic tan. The melanotans are potent, non-selective melanocortin receptor

agonists affecting MC1, MC3, MC4 and MC5 receptors. These receptors are responsible for many physiological systems including: pigmentation, energy, sexual function, immune system, inflammation and the cardiovascular system.

Melanotan II is a synthetic analogue of the  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH).  $\alpha$ -MSH is a melanocortin I receptor agonist which has a role in human pigmentation by stimulating production of eumelanin. As melanotan II is a non-specific melanocortin receptor agonist, it has been reported to cause toxicity effects involving the many physiological systems affected by the receptors.

Melanotan II was originally developed as a treatment for sexual dysfunction. However, this was abandoned when the metabolite bremelanotide was developed instead for treatment of haemorrhagic shock. Melanotan II is usually injected subcutaneously for the purposes of sunless tanning, appetite suppression, inducing sexual desire and penile erection and other conditions such as rosacea and fibromyalgia. There are also dose forms available for nasal administration. The therapeutic dose is considered to be 0.01 mg/kg.

### *Toxicity*

Toxicity effects of melanotan II from therapeutic and overdose exposures include renal dysfunction, rhabdomyolysis, sympathomimetic overdrive, change in size and pigmentation of pre-existing moles, rapid increase in the number of new moles, associated with causing melanomas, posterior reversible encephalopathy syndrome, refractory priapism, stretching and yawning syndrome, shortness of breath, chest pain, abdominal cramping and pain, dizziness and lethargy.

XXXXXX experience shows overdose appears to be relatively common, with the most frequent observation being a 10 fold overdose error resulting in toxicity symptoms and some have required hospitalisation.

### *Stability and contamination*

There are reports that these products have tested positive for microbial contaminants. After reconstitution, these vials are marketed for multiple uses for up to a few weeks, which pose a stability issue and further increase the infection risk issue.

### *Current use pattern in Australia*

Melanotan II tanning injections have received media attention over the past few years and have been dubbed the "barbie drug" by XXXXXX. The XXXXXX website states that all products are manufactured and compounded in pharmacies in Australia and, pending the satisfactory completion of a short medical assessment, will express post products to a nominated shipping address. The XXXXXX website also states that melanotan II is defined as a 'more potent peptide' when compared to melanotan I, offering a greater density in peptide chain with noticeable results in a shorter timeframe. There are also claims of enhancing male libido, sexual performance, curing erectile dysfunction and as an appetite suppressant.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACMS advice to the delegate***

The committee recommended that a new Schedule 4 entry, along with cross referencing to alpha-melanocyte stimulating hormone in the Index, be created for melanotan II.

#### **Schedule 4 - New Entry**

**MELANOTAN II.**

#### **Index - New Entry**

## MELANOTAN II

cross reference:  $\alpha$ -MELANOCYTE STIMULATING HORMONE

### Schedule 4

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the advice comprised the following:

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

- Risks: Advertising is currently leading consumers to purchase the product for lifestyle purposes, e.g. sunless tanning and appetite suppression, sexual stimulation. There is potential for numerous adverse events and toxicity, microbial contamination and unsafe needle and syringe handling.
- Melanotan II can be of unknown quality and subject to contamination and stability concerns with use of multi-dose vials. There is no experience with the product other than through unregulated channels. There are health risks from the substance itself and its route of administration – documented in medical literature, case reports as well as reports from NSW PIC.
- Benefits: There is no body of evidence demonstrating therapeutic benefits of melanotan II.

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

- Used by consumers, after purchase through unregulated online sites, for lifestyle enhancement/cosmetic purposes, e.g. sunless tanning, sexual enhancement and appetite suppression; these claims are unproven.
- The melanotan II product seems to be attractive to many consumers based on blogs and internet discussions.
- There have been warnings from regulators that a large numbers of unlicensed product suppliers have been closed (MHRA, FDA warnings).
- Not assessed for quality, safety and efficacy.
- Extent of use is unregulated and unquantified.

c) the toxicity of a substance:

- Melanotan II has a vast range of adverse effects related to therapeutic and overdose exposures. Toxicity data is limited.
- Toxicity is largely based on case reports and reports from the regulatory authorities (NSW PIC also submitted reports).
- Toxicity includes renal dysfunction, rhabdomyolysis, sympathomimetic overdrive, change in size and pigmentation of new moles, with one report of melanoma associated with use of melanotan II. Other case reports include posterior reversible encephalopathy syndrome (consisting of seizures, visual disturbance, confusion, headache, vomiting); refractory priapism, stretching and yawning syndrome; shortness of breath, chest pain, abdominal cramping & pain, dizziness and lethargy.

- There are also concerns with overdoses and infection risk from dosing errors, contamination, stability of multi-dose vials and poor injection technique. Most issues of use resolve and are reversible although some are serious and require hospitalisation.

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

- Product is supplied as a vial for reconstitution with water for injections.
- Injection – for SC use using an insulin-type needle. Unreferenced therapeutic dosage is thought to be 0.01 mg/kg. Dosing errors seem common.
- There are concerns with product quality, unregulated packaging, labelling, formulation and presentation. Concerns exist with unregulated product and perception of safety based on advertising.

e) the potential for abuse of a substance:

- Melanotan II is currently being used for unapproved and/or unregistered indications in an unregulated setting. Reports that the substance is abused for appetite suppression and sexual stimulation are limited.

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

- Other comparable regulators have issued warnings about its use.
- Possible public health issues in relation to claims on supplier websites that this substance can protect skin from sun damage.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

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

### ***Delegate's interim decision***

The delegate's interim decision is to include melanotan II in Schedule 4. The proposed Schedule entry is:

#### **Schedule 4 – New Entry**

MELANOTAN II.

#### **Index – New Entry**

#### **MELANOTAN II**

cross reference:  $\alpha$ -MELANOCYTE STIMULATING HORMONE

Schedule 4

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

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

The reasons for the recommendation comprised the following:

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

- Risks: Advertising is currently leading consumers to purchase the product for lifestyle purposes, e.g. sunless tanning and appetite suppression, sexual stimulation. There is potential for numerous adverse events and toxicity, microbial contamination and unsafe needle and syringe handling.
- The product can be of unknown quality and subject to contamination and stability concerns with use of multi-dose vials. There is no experience with the product other than through unregulated channels. There are health risks from the substance itself and its route of administration – documented in medical literature, case reports as well as reports from NSW PIC.
- Benefits: There is no body of evidence demonstrating therapeutic benefits of melanotan II.

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

- Used by consumers, after purchase through unregulated online sites, for lifestyle enhancement/cosmetic purposes, e.g. sunless tanning, sexual enhancement and appetite suppression; these claims are unproven.
- The melanotan II product seems to be attractive to many consumers based on blogs and internet discussions.
- There have been warnings from regulators that a large numbers of unlicensed product suppliers have been closed (MHRA, FDA warnings).
- Not assessed for quality, safety and efficacy.
- Extent of use is unregulated and unquantified.

*c) the toxicity of a substance:*

- Melanotan II has a vast range of adverse effects related to therapeutic and overdose exposures. Toxicity data is limited.
- Toxicity is largely based on case reports and reports from the regulatory authorities (NSW PIC also submitted reports).
- Toxicity includes renal dysfunction, rhabdomyolysis, sympathomimetic overdrive, change in size and pigmentation of new moles, with one report of melanoma associated with use of melanotan II. Other case reports include posterior reversible encephalopathy syndrome (consisting of seizures, visual disturbance, confusion, headache, vomiting); refractory priapism, stretching and yawning syndrome; shortness of breath, chest pain, abdominal cramping & pain, dizziness and lethargy.
- There are also concerns with overdoses and infection risk from dosing errors, contamination, stability of multi-dose vials and poor injection technique. Most issues of use resolve and are reversible although some are serious and require hospitalisation.

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

- Product is supplied as a vial for reconstitution with water for injections.
- Injection – for SC use using an insulin-type needle. Unreferenced therapeutic dosage is thought to be 0.01 mg/kg. Dosing errors seem common.

- There are concerns with product quality, unregulated packaging, labelling, formulation and presentation. Concerns exist with unregulated product and perception of safety based on advertising.

e) the potential for abuse of a substance:

- Melanotan II is currently being used for unapproved and/or unregistered indications in an unregulated setting. Reports that the substance is abused for appetite suppression and sexual stimulation are limited.

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

- Other comparable regulators have issued warnings about its use.
- Possible public health issues in relation to claims on supplier websites that this substance can protect skin from sun damage.

## 1.8 Orphenadrine

### ***Referred scheduling proposal***

An application was submitted to amend the Schedule 4 entry and create a new Schedule 3 entry for orphenadrine in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### ***Scheduling application***

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

#### **Schedule 3 – New Entry**

**ORPHENADRINE in oral preparations containing 35 mg or less of orphenadrine:**

- a) when compounded with not more than 500 mg paracetamol for the relief of pain associated with skeletal muscle spasm in adults and children 12 years of age and over; and**
- b) in a primary pack containing 24 or less dosage units.**

#### **Schedule 4 – Amend Entry**

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

The applicant's reasons for the request are:

- Orphenadrine is a skeletal muscle relaxant. Its citrate salt is used to relieve pain due to muscle spasm. Paracetamol is an analgesic. The combination of a skeletal muscle relaxant and an analgesic is useful in conditions where pain is associated with muscle spasm. The individual substances relieve the two defining symptoms of the targeted indication (pain and muscle spasm) and contribute to the clinical effect via different modes of action.
- Orphenadrine containing tablets have been available in Australia as a Schedule 4 medicine for over 40 years, and have a known efficacy and safety profile.
- The combination of orphenadrine 35 mg and paracetamol 450 mg provides effective relief of pain associated with muscle spasm including painful muscular conditions, musculoskeletal spasm, sports muscle injuries, lower back ache and muscle contraction headaches. It is useful in helping to break the pain-spasm-pain cycle resulting from minor trauma or injury.
- Painful musculoskeletal conditions are readily recognisable by the consumer. They are generally self-limiting and suitable for short-term treatment under the supervision of a pharmacist.



- Orphenadrine is an alternative treatment that provides a specific treatment for muscle spasms without the risks associated with low-dose non-steroidal anti-inflammatory drugs (NSAIDs) and codeine.
- Post codeine up-scheduling, there will be fewer preparations available for pharmacist's to recommend for painful musculoskeletal conditions.
- Treatment of muscle spasm with a combination of orphenadrine and paracetamol helps avoid undue immobilisation and consequential loss of work/other activities of daily living.
- Adverse effects associated with the combination are mainly due to the anticholinergic activity of orphenadrine and are more likely to occur at doses higher than proposed for the Schedule 3 entry. The safety of the combination is comparable to that of other anticholinergic medicines. Orphenadrine can potentially cause adverse effects such as dry mouth, palpitations, confusion and dizziness in elderly people. These effects are reversible and are usually mild and self-limiting at the recommended dosage. They can be managed by reducing the dose.
- The risk-benefit profile for the fixed dose regimen is positively supported with clinical trial evidence of up to 10 weeks treatment and includes comparison with the single actives.
- There are over 45 years of global post-marketing surveillance with orphenadrine. Its safety profile is comparable to that of other over-the-counter (OTC) medicines with anticholinergic activity. The safety profile of paracetamol is well known and does not appear to be affected by orphenadrine.
- There is a low level of relative risk associated with the rescheduling of orphenadrine when used in combination with paracetamol. Many products with anticholinergic activity are already available as Schedule 2 medicines for use in adults (e.g. hyoscine or diphenhydramine) and are often used with paracetamol-containing products. Pharmacists are familiar with counselling and educating consumers on the use of such medicines. Additionally, paracetamol is available as a general sales medicine in packs of 20 tablets, with larger packs up to 100 tablets available in pharmacies. Thus, pharmacists are already counselling patients on the use of anticholinergics and analgesics as separate medications. The counselling appropriate for a paracetamol and orphenadrine combination is consistent with that applied for the separate medicines.
- Strategies to minimise associated risks with a paracetamol and orphenadrine combination are:
  - Pack size restriction;
  - Inclusion of warning and precautionary statements in the product information (PI), consumer medicines information (CMI) and on the carton; and
  - Mandatory intervention by a pharmacist at point of sale to help minimise the potential for adverse effects and misuse.
- The proposed medicine label for the proposed product will comply with the new TGO92 medicine labelling orders set by the TGA, which will show all active ingredients prominently on the label thereby helping to minimise inadvertent misuse.
- The proposed product (same formulation as the Australian product) has been available in several countries, although not always concurrently. In South Africa, the proposed product has been an OTC medicine since 1978.
- The proposed product is a rational combination analgesic product fulfilling the unmet clinical need for an accessible OTC preparation supervised by the pharmacist that:
  - Specifically addresses both pain and muscle spasm;
  - Is without the risks associated with NSAIDs and codeine; and
  - Contains a total daily therapeutic dosage of 2.7 g paracetamol, well under the maximum 4 g recommended daily dosage considered safe by regulatory authorities worldwide and in published literature.

- The 4 day supply pack of the proposed product limits the amount of paracetamol intake. Pharmacists in their mandatory interventionist role as provider of Schedule 3 medicines will counsel individuals against co-administering other paracetamol containing products while taking the proposed product. This precaution will also appear on the label.
- The proposed Schedule 3 pack provides a maximum of 4 days treatment for painful musculoskeletal conditions associated with muscle spasm.
- Orphenadrine has nearly 40 years' experience in Australia and over 40 years' experience internationally.
- Safety record supported by longstanding Periodic Safety Update Reports (PSURs) and Database of Adverse Event Notifications (DAEN) data.
- Dedicated educational support programme for pharmacists by the sponsor and the Pharmaceutical Society of Australia including the best practice clinical protocol for pharmacists.

### ***Current scheduling status***

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

#### **Schedule 4**

ORPHENADRINE.

Paracetamol is currently listed in Schedules 2, 3 and 4 of the Poisons Standard as follows:

#### **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 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.

### **Schedule 3**

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

### **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.

It is also included under the entry paracetamol in Appendix F with the following statements:

### **Appendix F, Part 3**

PARACETAMOL

Warning 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); and/or
- **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); and

- **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); and
- **100** (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist).

### ***Scheduling history***

In February 1987, orphenadrine was first scheduled. Based on a jurisdiction list of sedating drugs, orphenadrine was included in Appendix K by the Drugs and Poisons Scheduling Committee (DPSC).

In November 1987, the DPSC noted that orphenadrine was included in the list of substances requiring a child-resistant closure in TGO 20. The committee agreed this was appropriate, and that it should not be replicated in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP).

In June 2011, the ACMS considered a proposal to reschedule orphenadrine in dosage units containing less than 35 mg from Schedule 4 to Schedule 3 when combined with paracetamol in a pack size of 24 dosage units or less. The application was referred to an external evaluator, who recommended that the application be rejected.

In September 2011, the delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with the recommendations that the scheduling of orphenadrine and paracetamol in Schedule 4 of the Poisons Standard remained appropriate.

### ***Australian regulatory information***

The Australian Register of Therapeutic Goods (ARTG) has two entries for products registered containing both orphenadrine and paracetamol. The products differ in container presentation – blister pack vs. tablet bottle.

In the last 30 years there have been 39 reported cases of adverse events related to orphenadrine, and 3237 related to paracetamol in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 21 cases with the single suspected medicine being orphenadrine, and 1244 cases with paracetamol. Of these, no cases reported death as the outcome associated with orphenadrine, compared to 137 cases reported death as an outcome associated with paracetamol over the same 30 year period.

### ***International regulations***

Tablets containing orphenadrine citrate 100 mg (as the only active ingredient) are marketed as OTC in Canada.

Both Medsafe New Zealand and the United States of America's Food and Drug Authorisation classify orphenadrine citrate as a prescription medicine.

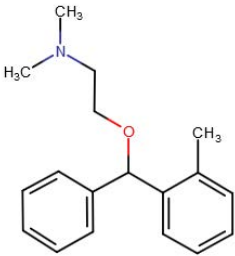
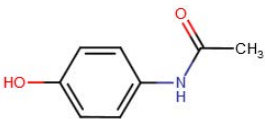
### ***Substance summary***

Orphenadrine is a congener of diphenhydramine. It is a tertiary amine antimuscarinic agent with weak antihistaminic and local anaesthetic properties. It also inhibits noradrenaline transport and blocks NMDA receptors and voltage-gated sodium channels.

Orphenadrine is a skeletal muscle relaxant. Its citrate salt is used to relieve pain due to muscle spasm. However, efficacy for this indication is not well established.

Paracetamol is an analgesic. The combination of a skeletal muscle relaxant and an analgesic is useful in conditions where pain is associated with muscle spasm. The individual substances relieve the two defining symptoms of the targeted indication (pain and muscle spasm) and contribute to the clinical effect via different modes of action.

### **Table 1.8.1: Chemical information of orphenadrine and paracetamol**

Property	Orphenadrine	Paracetamol
CAS number	83-98-7	103-90-2
IUPAC and/or common and/or other names	<i>N,N</i> -dimethyl-2-[(2-methylphenyl)-phenylmethoxy]ethanamine (IUPAC); 1S/C18H23NO/c1-15-9-7-8-12-17(15)18(20-14-13-19(2)3)16-10-5-4-6-11-16/h4-12,18H,13-14H2,1-3H3 (InChI); Orphenadrine (INN);	<i>N</i> -(4-hydroxyphenyl)acetamide (IUPAC); 1S/C8H9NO2/c1-6(10)9-7-2-4-8(11)5-3-7/h2-5,11H,1H3,(H,9,10) (InChI); Acetaminophen (USP);
Chemical structure		
Molecular formula	C <sub>18</sub> H <sub>23</sub> NO	C <sub>8</sub> H <sub>9</sub> NO <sub>2</sub>
Molecular weight	269.4 g/mol	151.2 g/mol

### ***Pre-meeting public submissions***

Five (5) public submissions were received, four (4) that oppose and one (1) that supports the scheduling proposal for orphenadrine.

#### *Main points in support:*

- The rescheduling proposal outlined is for short-term therapy. Although anticholinergic effects of orphenadrine may require some caution, the proposed dosage is low and orphenadrine has an overall well-established safety and efficacy profile.
- The proposed indication for Schedule 3 can be regarded to be recognisable by the patient.
- A pharmacist will be able to consider the patient's circumstance to discuss whether orphenadrine and paracetamol would be the most appropriate analgesic. The submitter also recognises that pharmacist education and relevant practice tools would be required for the implementation of Schedule 3.
- The orphenadrine and paracetamol combination product has been available in Australia for many years. However, pharmacists report it is not widely used. This may be due to low level awareness of prescribers since the product is not listed on the Pharmaceutical Benefits Scheme (PBS). Even if the product was an appropriate therapeutic option, patients may prefer other PBS-listed options.

#### *Main points opposed:*

- Orphenadrine is potentially very toxic in overdose.

- Orphenadrine has very limited role in pain management,<sup>39, 40</sup> poor efficacy and patients rapidly develop tolerance to this medicine.
- Orphenadrine has significant abuse potential and Inclusion in schedule 3 would allow greater access to orphenadrine for inappropriate use.
- Clinical toxicology and poison information units have experienced an increase in presentations with orphenadrine ingestion in recent years as the management of chronic pain turns its focus onto alternatives to opioids.
  - In the period 6/1/14 to 27/9/17 there have been 45 deliberate self-poisonings, 16 therapeutic errors and 11 accidental exposures involving orphenadrine.
  - Anecdotal recount from a pharmacist who has encountered a patient who had overdosed on orphenadrine resulting in ischaemic bowel and the formation of a stoma.
- Within the group of anticholinergic medications it appears to have the greatest risk of death as a result of ventricular dysrhythmias, respiratory depression, seizures and hypoglycaemia.<sup>41</sup> Orphenadrine is over represented in deaths when compared to other antimuscarinics or antipsychotics.
  - 71.5 deaths per million prescriptions compared to 0-6.1 deaths per million prescriptions for other anticholinergics.<sup>42</sup>
- Orphenadrine is not a high volume prescription item, and given that those who would benefit from it have conditions which should require medical management, there is no rationale for a proposal to down schedule.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that the current scheduling of orphenadrine remains appropriate.

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

The reasons for the advice comprised the following:

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

- Risks: there is significant abuse potential, increased occurrence of abuse episodes, OD-induced deaths, adverse cardiac events, drug-drug interactions, and incompatible pharmacokinetics with other drugs. There is also a lack of efficacy for certain claims for indications.
- Benefit: There is modest evidence of support as a skeletal muscle relaxant.

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

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<sup>39</sup> Chou R, Peterson K, Helfand M. (2004). Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *J Pain Symptom Manage.* Aug;28(2):140-75

<sup>40</sup> Richards BL, Whittle SL, Buchbinder R. (2012). Muscle relaxants for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev.* Jan 18;1:CD008922

<sup>41</sup> Dawson AH. Antimuscarinic drugs in Dart RC (ed). *Medical Toxicology* 3rd Ed.

<sup>42</sup> [Buckley and McManus \(1998\) 'Fatal toxicity of drugs used in the treatment of psychotic illnesses'. \*Br J Psychiatry.\* 172, 461](#)



- It is not a realistic alternative for those in whom NSAIDs are contraindicated or cautioned (e.g. those over 65) because this same group is also the most sensitive to the anticholinergic adverse effects of orphenadrine.
- Orphenadrine is claimed to be useful for painful conditions where muscle spasm is a component of the pain, such as sprains and strains, sports muscle injuries, whiplash, lower back ache and tension headaches. It is noted that there are no specific data on efficacy for most of these conditions.

c) the toxicity of a substance:

- There are documented cases of child poisoning with significant toxicity at doses of 6 tablets, and has been associated with fatalities in overdose (e.g. 80 fatalities in Sweden). For overdose, there is evidence that orphenadrine is more toxic than other anticholinergic drugs (Buckley and McManus 1998), and many fatalities have been reported (Jonsson *et al.*, 2004). Orphenadrine has also caused fatalities in children after accidental ingestion.
- Orphenadrine contributes to the anticholinergic burden.

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

- Because of the potential toxicity for children of orphenadrine products, these products need to be presented in child-resistant packing.
- The evaluator noted the applicant's statement that ingestion of 24 tablets as a single dose would have minimal potential for harm was incorrect, as 10.8 g of paracetamol could lead to serious or fatal hepatotoxicity, even in adults.
- The total content of 840 mg orphenadrine could cause serious problems in children (Van Herrewhege *et al.*, Intensive Care Med 1999; Garza *et al.*, Pediatr Emerg Care 2000).

e) the potential for abuse of a substance:

- There are some case reports of dependency and abuse (Shariatmadari, BMJ 1975; Schifano *et al.*, South Med J 1988; Mugglestone, Lancet 1985), but it does not appear to be a commonly abused substance. With wider use, if there were greater ease of access, this may change.

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

- The product has not been fully evaluated based on contemporary standards.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS 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 that the current scheduling of orphenadrine remains appropriate.

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



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

The reasons for the recommendation comprised the following:

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

- Risks: there is significant abuse potential, increased occurrence of abuse episodes, OD-induced deaths, adverse cardiac events, drug-drug interactions, and incompatible pharmacokinetics with other drugs. There is also a lack of efficacy for certain claims for indications.
- Benefit: There is modest evidence of support as a skeletal muscle relaxant.

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

- It is not a realistic alternative for those in whom NSAIDs are contraindicated or cautioned (e.g. those over 65) because this same group is also the most sensitive to the anticholinergic adverse effects of orphenadrine.
- Orphenadrine is claimed to be useful for painful conditions where muscle spasm is a component of the pain, such as sprains and strains, sports muscle injuries, whiplash, lower back ache and tension headaches. It is noted that there are no specific data on efficacy for most of these conditions.

c) the toxicity of a substance:

- There are documented cases of child poisoning with significant toxicity at doses of 6 tablets, and has been associated with fatalities in overdose (e.g. 80 fatalities in Sweden). For overdose, there is evidence that orphenadrine is more toxic than other anticholinergic drugs (Buckley and McManus 1998), and many fatalities have been reported (Jonsson *et al.*, 2004). Orphenadrine has also caused fatalities in children after accidental ingestion.
- Orphenadrine contributes to the anticholinergic burden.

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

- Because of the potential toxicity for children of orphenadrine products, these products need to be presented in child-resistant packing.
- The evaluator noted the applicant's statement that ingestion of 24 tablets as a single dose would have minimal potential for harm was incorrect, as 10.8 g of paracetamol could lead to serious or fatal hepatotoxicity, even in adults.
- The total content of 840 mg orphenadrine could cause serious problems in children (Van Herrewhege *et al.*, Intensive Care Med 1999; Garza *et al.*, Pediatr Emerg Care 2000).

e) the potential for abuse of a substance:

- There are some case reports of dependency and abuse (Shariatmadari, BMJ1975; Schifano *et al.*, South Med J 1988; Mugglestone, Lancet 1985), but it does not appear to be a commonly abused substance. With wider use, if there were greater ease of access, this may change.

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

- The product has not been fully evaluated based on contemporary standards.

## 1.9 Clotrimazole

### *Referred scheduling proposal*

An application was submitted to amend the Schedule 2 and Schedule 4 entries and to delete the Schedule 3 and Appendix H entries for clotrimazole in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

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

#### **Schedule 2 – Amend Entry**

CLOTRIMAZOLE for human use in **vaginal preparations**, dermal preparations and for application to the nails **except** in preparations for the treatment of tinea pedis.

#### **Schedule 3 – Delete Entry**

~~CLOTRIMAZOLE in preparations for vaginal use.~~

#### **Schedule 4 – Amend Entry**

CLOTRIMAZOLE **except**:

- a) when included in Schedule 2, ~~3~~ or 6; or
- b) in preparations for dermal use for the treatment of tinea pedis.

#### **Appendix F, Part 3 Warning Statements – Amend Entry**

CLOTRIMAZOLE in vaginal preparations when included in Schedule ~~3~~**2**.

#### **Appendix H –Delete Entry**

~~CLOTRIMAZOLE.~~

The applicant's reasons for the request are:

- Topical preparations containing clotrimazole are well-established as appropriate medicines for consumer self-selection, as demonstrated by their broad self-select availability in both pharmacy and non-pharmacy outlets in most markets worldwide.
- Clotrimazole vaginal preparations have been available in the USA and UK as an unscheduled medicine since 1990 and 2004 respectively, and have progressively been switched to general sale self-select medicines in other major markets.
- Clotrimazole has been available in Australia as a Schedule 2 medicine for the topical treatment of fungal infections since 1991. It is also an unscheduled medicine for dermal *tinea pedis* infections since 2005, with no new safety issues being identified.
- The predicted public health benefits from the proposal are an increase in women's health literacy and a facilitated positive shift in Australian women's intimate health management.
- Quality use of medicines can be achieved through well-designed labelling. There is a need to update the labelling of clotrimazole vaginal preparations to focus on accurate symptom identification including accurate self-treatment information and directions to consult a health care professional in cases of:
  - recurring episodes;
  - apparent atypical symptoms of vulvovaginal candidiasis;

- symptoms being indicative of another causative pathogen; or
- treatment failure.
- The rescheduling of vaginal clotrimazole to Schedule 2 will improve access and increase flexibility in self-selection of effective treatments for women with uncomplicated vulvovaginal candidiasis. Clotrimazole vaginal preparations have been available internationally in more than 70 countries as self-select medicines for almost 30-years without any evidence of safety issues. Whilst pharmacists are generally well-equipped and skilled at having personal conversations in private spaces, the down-scheduling proposal represents a long-overdue regulatory change resulting in an end to barriers to access and potential delays in treating vulvovaginal candidiasis for many Australian women.

### ***Current scheduling status***

Clotrimazole is currently listed in Schedules 2, 3, 4 and 6 and Appendices F and H of the Poisons Standard as follows:

#### **Schedule 2**

CLOTRIMAZOLE for human use in dermal preparations and for application to the nails **except** in preparations for the treatment of tinea pedis.

#### **Schedule 3**

CLOTRIMAZOLE in preparations for vaginal use.

#### **Schedule 4**

CLOTRIMAZOLE **except**:

- a) when included in Schedule 2, 3 or 6; or
- b) in preparations for dermal use for the treatment of tinea pedis.

#### **Schedule 6**

CLOTRIMAZOLE for the external treatment of animals.

Clotrimazole is also included in Appendix F and Appendix H as follows:

#### **Appendix F, Part 3**

CLOTRIMAZOLE in vaginal preparations when included in Schedule 3.

Warning Statements: 54 (Seek medical advice before first course of treatment); 63 (See a doctor if you are pregnant or diabetic); 64 (See a doctor (or) (dentist) if no better after (Insert number of days as per approved Product Information) days); 66 (See a doctor if problem returns).

#### **Appendix H**

CLOTRIMAZOLE.

### ***Scheduling history***

Clotrimazole was first scheduled in August 1977. Clotrimazole has an extensive scheduling history since 1985. The scheduling history relevant to vaginal preparations have been presented below.

The August 1977, the Drugs and Poisons Schedule Standing committee (DPSSC) included clotrimazole in Schedule 4.

In April 1994, the National Drugs and Poisons Schedule Committee (NDPSC) agreed to down-schedule preparations of clotrimazole for vaginal use to Schedule 3 to give its current entry. Following out-of-

session consideration, the committee also agreed to include the current warning statements in Appendix F for clotrimazole when included in Schedule 3.

In November 1996, the NDPSC considered a submission to reschedule clotrimazole for vaginal use to Schedule 2. The committee did not support the rescheduling application.

In February 1997, the NDPSC considered the post-meeting comment concerning the November 1996. The committee agreed that the November 1996 decision remained appropriate and that clotrimazole for vaginal use should remain in Schedule 3.

In August 1998, the NDPSC considered a submission to include miconazole in Appendix H, and decided to allow other antifungals currently included in Schedule 3 to be advertised by including them in Appendix H. These substances were clotrimazole, econazole, miconazole and nystatin.

In February 2006, the NDPSC considered a submission to reschedule clotrimazole for vaginal use to Schedule 2. After consideration of the new data presented, the committee agreed that the current scheduling of clotrimazole remained appropriate. The committee noted that maintaining mandatory pharmacist involvement in the sale of clotrimazole was needed to fully address the committee's concerns, particularly the risk of repeated clotrimazole use masking an underlying serious condition.

In February 2007, the NDPSC considered a submission to reschedule clotrimazole for vaginal use to Schedule 2. The committee agreed that the current scheduling of clotrimazole for vaginal use remained appropriate. Maintaining mandatory pharmacist involvement in the sale of clotrimazole was needed to fully address the committee's concerns, particularly the risk of repeated clotrimazole use masking an underlying serious condition without referral to a pharmacist or doctor or being used incorrectly on non-fungal vaginal infections or conditions.

### ***Australian regulatory information***

Clotrimazole is listed in 85 entries on the Australian Register of Therapeutic Goods (ARTG). The products marketed include creams in varying strengths and quantities (including in combination with hydrocortisone), capsules for oral use and pessaries for internal use.

In the last 30 years there have been 141 adverse event reports in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 95 cases with a single suspected medicine and no cases resulting in death.

According to the [TGA Ingredient Database](#), clotrimazole is available for use as an:

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

### ***International regulations***

#### *New Zealand*

Clotrimazole is listed as a prescription medicine in New Zealand, with the exception of preparations for vaginal (restricted) or external use (Pharmacy Only and General Sale).

#### *United States of America (USA)*

The USA Food and Drug Administration regulate preparations of clotrimazole as prescription and over-the-counter medicines, based on formulation type and indication. There are a number of lozenges and creams available on prescription, with creams for internal use available over-the-counter.

#### *Canada*

Clotrimazole vaginal preparations are available over-the-counter in Canada.

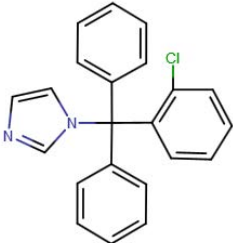
## European Union (EU)

Clotrimazole is listed in Annex I in the EU for cutaneous use at 1% w/w.

### Substance summary

Clotrimazole is an antimycotic drug with activity against the yeast *Candida albicans*, and lesser activity against other species of *Candida*. It was first approved in Australia 50 years ago for topical use, and has continued to be available for treatment of mucocutaneous fungal infections in dermal creams and solutions and vaginal creams and pessaries.

**Table 1.9.1: Chemical information of clotrimazole**

Property	Clotrimazole
CAS name	Clotrimazole
CAS number	23593-75-1
IUPAC and/or common and/or other names	1-[(2-chlorophenyl)-diphenylmethyl]imidazole (IUPAC); Clotrimazole (INN);
Chemical structure	
Molecular formula	C <sub>22</sub> H <sub>17</sub> ClN <sub>2</sub>
Molecular weight	344.8 g/mol

### Pharmacology

Clotrimazole is an imidazole derivative with a broad spectrum antimycotic activity arising from inhibition of ergosterol synthesis. This leads to structural and functional impairment of the cytoplasmic membranes of dermatophytes, yeasts and moulds.

Clotrimazole is an antimycotic drug with excellent activity against *Candida albicans*, and lesser activity against other species of *Candida*. Clotrimazole also acts on *Trichomonas vaginalis*. The minimum inhibitory concentration (MIC) is approximately 10-1000 times greater than for *Candida albicans*. With MICs intermediate to that of *Candida* sp. and *Trichomonas vaginalis*, clotrimazole also have activity on gram-positive (*Streptococci* sp. / *Staphylococci* sp.) and gram-negative bacteria (*Bacteroides* sp. / *Gardnerella vaginalis*).

Primarily-resistant fungal variants to clotrimazole are very rare, and secondary fungal resistance has only been observed in very isolated cases.

A maximum of 10% of the dose of vaginally applied clotrimazole is said to be absorbed systemically. Various pharmacokinetic studies with XXXXXX pessaries demonstrated maximum clotrimazole plasma concentrations 10 to 72 hours post administration of only 10 µg/mL. Similar maximum plasma concentrations were detected after application of XXXXXX vaginal cream.

Clotrimazole is metabolised extensively in the liver to inactive compounds. The primary route of excretion is likely to be via the faeces, given urinary excretion of dermally-applied XXXXXX cream.

## Toxicity

No carcinogenicity or mutagenicity has been observed in animal studies. Administration of XXXXXX vaginal preparations to a small number of women in the 2nd and 3rd trimesters of pregnancy was not associated with obvious untoward effects on the course of the pregnancy or on the foetus.

Clotrimazole is classified as a pregnancy Category A medicine. There are no contraindications, other than hypersensitivity, for XXXXXX vaginal preparations. There are no precautions for use that have urgent/serious clinical consequences with common and/or high-risk coexisting diseases, treatments or conditions.

## Current use pattern in Australia

Medications available in Australia are now limited to formulations for topical treatment and prevention of mucocutaneous fungal infections. Dermal creams and solutions are commonly used for fungal skin infections including tinea pedis, nappy rash, candidal balanoposthitis and facial, flexural or scrotal seborrheic dermatitis. Vaginal clotrimazole creams and pessaries are used to treat vulvovaginal candidiasis which is primarily caused by *Candida albicans*. Atypical *Candida sp.* is isolated in only 5% of women with vulvovaginal candidiasis (VVC).

## Pre-meeting public submissions

Five (5) public submissions were received, one (1) that supported and four (4) that opposed the scheduling proposal.

### Main points in support:

- Clotrimazole is effective and has a well-established safety profile.
  - Clotrimazole is an antimycotic drug with proven efficacy against *Candida albicans*, and lesser activity against other species of *Candida*.
  - VVC is a prevalent women's health issue, with 70-75% of women experiencing at least one episode (and with 82% of women with VVC being repeat sufferers). VVC is also a source of embarrassment, with this embarrassment being reported as a contributing factor leading to delays in seeking treatment. However, the symptoms of VVC are easily recognised and can be simply treated with clotrimazole.
- Identification and treatment of VVC, without mandatory recourse to a pharmacist, is something that consumers can reasonably be expected to manage.
  - Clotrimazole was first approved in Australia 50 years ago for topical use and continues to be available for the treatment of mucocutaneous fungal infections, in dermal creams, solutions, vaginal creams and pessaries.
  - Clotrimazole has been available in Australia as a Schedule 2 medicine for the topical treatment of fungal infections since 1991, and as an unscheduled medicine for dermal *tinea pedis* infections since 2005.
  - The long history of Schedule 3 availability means that women will be familiar with the product and not all women will require pharmacist counselling at the point of purchase.
- Clotrimazole in vaginal preparations meets the scheduling factors for Schedule 2 medicines as set out in the Scheduling Policy Framework (SPF):
  - Women who have been previously diagnosed with VVC will be capable of recognising their VVC symptoms without pharmacist verification.
  - Clotrimazole has a well-established safety profile, low systemic absorption when used vaginally and there are no reports of *Candida spp.* resistance.
  - There is no evidence of dependence, misuse or abuse.



- Clotrimazole has a well-established safety profile and a very low ADR rate.
- While the risk of masking a serious disease is low, there is a risk of delaying the diagnosis of a non-Candidal infection by a few days. It is very unlikely, however, that a short delay in diagnosis will have any material impact on the clinical prognosis of any likely alternative conditions. This risk will not be appreciably altered by a change from Schedule 3 to Schedule 2 availability and can be easily managed through label content.
- Amending the scheduling as proposed would bring Australian's access to clotrimazole into line with other comparable markets.
  - Clotrimazole is available over-the-counter (without mandatory pharmacist intervention) in more than 70 other countries (and is available as a general sale item – GSL - in the US and the UK).

*Main points opposed:*

- Patients presenting with vaginal disorders should consult a pharmacist to ensure that the diagnosis and treatment is appropriate and/or necessary. This will ensure the best option for optimal patient health outcomes.
- Pharmacists are able to refer patients to doctors when appropriate. For example when patients are diabetic, under 16, over 60 years of age, pregnant, taking immunosuppressants, or when other vaginal conditions may be suspected.
- Pharmacist's advice can assist in considering the patient's symptoms, treatment history, current medications and other health conditions.
- Consultation with a pharmacist is also important to rule out common differential diagnoses such as bacterial vaginosis, candida vaginitis and trichomoniasis which have different first-line treatment options. The use of antifungal products in non-fungal vaginal infections is ineffective, may worsen the condition, and can delay diagnosis and commencement of appropriate therapy.
- While vaginal candidiasis may be self-diagnosed in some cases, studies have shown that caution is required due to concerns around the accuracy of self-diagnosis.<sup>43, 44</sup> Tenni *et al.*,<sup>44</sup> cited figures and findings from other research reports as follows:
  - Of women who presented with a self-diagnosed initial episode of candidiasis, only 59% actually had the condition.
  - Only 34% who self-diagnosed vaginal candidiasis were correct.
  - Women who had previously had an episode of clinically diagnosed vaginal candidiasis were no more accurate in their diagnosis than women without previous episodes.
- Pharmacists can advise on the management of repeated episodes or vaginal candidiasis and provide recommendations on ways to minimise the risk of vaginal infections in the future.
  - Studies indicate that the relapse rate for these types of infections is high, possibly due to poor diagnosis.<sup>45</sup>

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<sup>43</sup> Ryan-Wenger NA, Neal JL, Jones AS *et al.*. Accuracy of vaginal symptom self-diagnosis algorithms for deployed military women. *Nurs Res* 2010;59(1):2-10.

<sup>44</sup> Tenni P, Hughes J, McCloskey J, Hilmi S. Ensuring the appropriateness of topical over-the-counter antifungal agents for clients with self-diagnosed vaginal thrush (the TAFT Project). *Canberra: Pharmacy Guild of Australia*; 2005.

<sup>45</sup> Schwiertz, Andreas, *et al.*. "Throwing the dice for the diagnosis of vaginal complaints?." *Annals of clinical microbiology and antimicrobials* 5.1 (2006): 4.



- The risk of inaccurate self-diagnosis and subsequent delay in treatment for more serious underlying conditions warrants the continued mandatory oversight of a pharmacist. A pharmacist can also discuss more suitable treatment options where required.
- A 2002 study<sup>46</sup> showed only a third of women who self-diagnosed vaginal candidiasis were accurate and that prior clinician-based diagnosis and reading the label do not improve women's ability to properly diagnose vulvovaginal candidiasis.
- Inclusion in Schedule 2 would allow greater access and therefore an increased likelihood of errors with oral treatments for vaginal thrush. These errors may result in possible gastrointestinal symptoms from ingestions of the pessary, but more importantly result in delays in effective treatment for the patient, leading to increased discomfort from and duration of symptoms.
- Poisons information centres continue to receive calls from members of the public who have inadvertently ingested the vaginal pessary. Current packaging is not sufficiently clear and the word "pessary" is not widely understood in the community to ensure patients are using these products correctly.
  - Current risks could be minimised by improved packaging and labelling to clarify method of administration and training of pharmacists to clarify administration method with the patients at the time of purchase.
- The economic cost of these errors is seen in cost of additional treatment for the patient, increased sick leave and greater use of health resources in the form of GP visits, hospital presentation and calls to poison information centers.
- While some woman may feel uncomfortable discussing such conditions with a pharmacist or have privacy concerns, this is not a sufficient reason to down-schedule clotrimazole in vaginal preparations, particularly given the risks. The majority of pharmacies have private consultation areas and pharmacies are encouraged to offer these areas to consumers where appropriate. Consumers can also request to have these conversations discreetly in a more private area.
  - June 2017 Pharmacy Board of Australia registrant data<sup>47</sup> indicates that the majority of registered pharmacists are female. In most cases, this should enable consumers to speak with a female pharmacist if they are more comfortable discussing this condition with a pharmacist of the same gender.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACMS advice to the delegate***

The committee recommended that the scheduling of clotrimazole remains appropriate.

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

The reasons for the advice comprised the following:

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

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<sup>46</sup> Ferris DG, Nyirjesy P, Sobel JD *et al.*; Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis; *Obstetrics & Gynecology* 2002; 99:419-425

<sup>47</sup> [The Pharmacy Board of Australian June 2017 Statistics](#)

- Risks: the major risk is from inaccurate self-diagnosis, or delayed treatment if the product is used to treat other vaginal infections not caused by *Candidia albicans*.
- Benefits: clotrimazole is a safe and effective treatment for vulvovaginal candidiasis caused by *Candidia albicans*.

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

- Clotrimazole in vaginal preparations are used to treat uncomplicated vulvovaginal candidiasis caused by *Candidia albicans*.
- It is a first-line treatment for vulvovaginal candidiasis in current Australian guidelines along with intravaginal nystatin cream, intravaginal miconazole and oral fluconazole.

c) the toxicity of a substance:

- Low potential toxicity.

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

- Warning statements are already required for clotrimazole vaginal preparations. More detailed information on when a health professional should be consulted and the likely symptoms of conditions that will not respond to clotrimazole are proposed. However, there is evidence that women do not read the package information and that reading the label does not improve the accuracy of self-diagnosis.
- The packaging of vaginal pessaries has been associated with an increase in oral ingestion of the pessaries. This proposal does not address this poisoning risk.

e) the potential for abuse of a substance:

- Low potential for abuse.

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

- Clotrimazole vaginal preparations are currently included in Appendix H. The company is free to make the educational campaign that they propose.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS 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 that the current scheduling of clotrimazole remains appropriate.

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

The reasons for the recommendation comprised the following:

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

- Risks: the major risk is from inaccurate self-diagnosis, or delayed treatment if the product is used to treat other vaginal infections not caused by *Candidia albicans*.
- Benefits: clotrimazole is a safe and effective treatment for vulvovaginal candidiasis caused by *Candidia albicans*.

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

- Clotrimazole in vaginal preparations are used to treat uncomplicated vulvovaginal candidiasis caused by *Candidia albicans*.
- It is a first-line treatment for vulvovaginal candidiasis in current Australian guidelines along with intravaginal nystatin cream, intravaginal miconazole and oral fluconazole.

c) the toxicity of a substance:

- Low potential toxicity.

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

- Warning statements are already required for clotrimazole vaginal preparations. More detailed information on when a health professional should be consulted and the likely symptoms of conditions that will not respond to clotrimazole are proposed. However, there is evidence that women do not read the package information and that reading the label does not improve the accuracy of self-diagnosis.
- The packaging of vaginal pessaries has been associated with an increase in oral ingestion of the pessaries. This proposal does not address this poisoning risk.

e) the potential for abuse of a substance:

- Low potential for abuse.

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

- Clotrimazole vaginal preparations are currently included in Appendix H. The company is free to make the educational campaign that they propose.

## 2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS/ACMS #17)

### Summary of delegates' interim decisions

Substance	Interim Decision
Helium	Helium does not require scheduling.
Salts of Boric Acid	<p><b>Schedule 5 – Amend Entry</b></p> <p><b>BORIC ACID except:</b></p> <ul style="list-style-type: none"> <li>a) when included in Schedule 4; or</li> <li>b) in preparations, other than insect baits, containing 1 per cent or less calculated as boron; or</li> <li>c) in hand cleaning preparations.</li> </ul> <p><b>Index – Amend Entry</b></p> <p><b>BORIC ACID</b> cross reference: BORAX, BORON</p> <p><i>The proposed implementation date is 1 October 2018.</i></p>
Polihexanide	<p><b>Schedule 6 – Amend Entry</b></p> <p><b>POLIHEXANIDE except:</b></p> <ul style="list-style-type: none"> <li>a) in cosmetic preparations containing 0.3 per cent or less of polihexanide; or</li> <li>b) when packed and labelled for therapeutic use, or</li> <li>c) in other preparations containing 5 per cent or less of polihexanide.</li> </ul> <p><b>Appendix F, Part 3 – Amend Entry</b></p> <p>POLIHEXANIDE</p> <p>Warning Statement: 28 (Repeated exposure may cause sensitisation).</p> <p>Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist).</p> <p><b>Index Entry – Amend Entry</b></p> <p><b>POLIHEXANIDE</b> cross reference: 1-(diaminomethylidene)-2-hexylguanidine, poly(iminocarbonimidoyliminocarbonimidoyl imino-1,6-hexanediyl), polyhexamethylene biguanide (PHMB)</p> <p>Schedule 6 Appendix E, Part 2 Appendix F, Part 3</p>

	<i>The proposed implementation date is 1 June 2018.</i>
Cimicoxib	<p><b>Schedule 4 – New Entry</b></p> <p>CIMICOXIB.</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>

## 2.1 Helium

### *Referred scheduling proposal*

An application was submitted by the Australian Competition and Consumer Commission (ACCC) to include helium gas in Schedules 6 and 7, and Appendices E and F in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard. The ACCC proposed that helium gas in pressurised gas canisters or cylinders sold or hired to consumers for household or domestic use must contain an aversive and that the supply of helium gas for commercial and industrial uses would not require an aversive, but its supply would be restricted by scheduling.

### *Scheduling application*

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

#### **Schedule 6 – New Entry**

HELIUM GAS in pressurised gas canisters or cylinders sold or hired for household or domestic use and containing XX mg/kg, XX ppm or XX mg/m<sup>3</sup> XXXXXXXXXXXXXXXX of an aversive agent.

#### **Schedule 7 –New Entry**

HELIUM GAS, **except** when included in Schedule 6.

#### **Appendix E, Part 2 – New Entry**

Standard Statements A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), G1 (Urgent hospital treatment is likely to be needed), R1 (If inhaled, remove from contaminated area. Apply artificial respiration if not breathing).

#### **Appendix F, Part 1 – New Entry**

Warning Statement: 109: May be fatal if inhaled.

This is a truncated version of statement 13 with the words, ‘swallowed or absorbed through skin’ omitted.

110: Inhalation may cause brain damage.

#### **Appendix F, Part 3 – New Entry**

Warning Statement: 15 (Liquid will cause burns); 109 (May be fatal if inhaled) [new]; 110 (Inhalation may cause brain damage) [new].

The applicant’s reasons for the request are:

- The ACCC makes this proposal having regard to the safety risks associated with the supply of helium as a consumer good and following correspondence from the Victorian Coroner. The Victorian Coroner has requested that the ACCC investigate the supply of helium gas and recommended the restriction of the ease of access to helium gas by the Australian public.

- Helium gas has known potential for misuse. The substance is a simple asphyxiant. Inhalation of helium gas has a high potential for causing harm (including death) at relatively low exposure and without warning of the asphyxiation effect. The substance is colourless, odourless and tasteless. Asphyxiation by this substance occurs very quickly and occurs through the displacement of oxygen by helium in the lungs. This may result in brain damage and death, with rescue being unlikely.
- Asphyxiation by inert gases, including helium, is widely publicised as a certain, quick, simple, painless and non-disfiguring method of suicide.
  - Asphyxiation with helium gas is an increasingly popular method of suicide in Australia since 2000. There have been an estimated 400 suicides using helium gas between 2000 and 2016 (an average of about 24 each year). The number of cases gradually increased between 2000 and 2009, but more than doubled in 2009-10, increasing from 23 to 50 cases each year. The higher number of helium asphyxiation suicides per year has been relatively steady since 2010, at about 45 cases per year.
- Helium gas canisters or cylinders, and other equipment used to commit suicide by this method, are readily available to the public and information about the method is easily found on the internet.
  - According to information in the national coronial database, the main sources of helium used for suicides are party goods suppliers (76 per cent) and industrial gas suppliers (14 per cent).
  - Helium is supplied to Australian householders for the purpose of inflating balloons or similar novelty items. Small non-refillable and disposable helium canisters are available for purchase in retail outlets. In addition, larger helium cylinders are available for hire for the same purpose from party supply stores and some suppliers of industrial gases.
- Adding an aversive to helium gas sold to consumers is expected to reduce its misuse/abuse for suicide. It should also reduce other forms of dangerous misuse, such as 'huffing' and deliberately inhaling the gas from balloons to achieve a squeaky voice effect.
- This proposal does not seek any amendments to Parts 1-3 of the *Poisons Standard* (Controls and Regulations). However, the ACCC highlights a potential supplementary application to amend the presentation and packaging of the product to require more complex or difficult to use fixings through a change to Parts 1-3 of the *Poisons Standard*.
- The ACCC is seeking assistance from the bottled gas industry and helium suppliers, regarding potential changes to the valve and nozzle arrangement on helium canisters and cylinders that are sold to or hired by consumers for balloon inflation. These negotiations are aimed at having the bottled gas industry make a voluntary change to the operation of these fittings, so that gas is more difficult for adults and children to get out of the cylinder or canister. This change is considered secondary to the inclusion of an aversive in domestic supplies of helium. If this change requires the amendment of a voluntary standard (for gas cylinders), it is likely to be time-consuming and needs to be driven by the bottled gas industry itself. If imported helium canisters are to be fitted with different fixings, this will require a supplementary application to amend the *Poisons Standard*, as these products do not appear to be required to comply with Australian Standards.
- As helium gas is currently not scheduled, no First Aid Instructions or Safety Directions are required, due to the general exemption for unscheduled substances.
- The proposed scheduling arrangement will not affect commercial, industrial or medical uses of helium. Helium gas for sale in pre-inflated balloons (e.g. through a party hire business) would not be affected, as this is a commercial use of helium. Helium gas containing an aversive would be freely available for sale or hire by consumers to use in their homes to inflate balloons and similar novelties.

### ***Current scheduling status and relevant scheduling history***

Helium gas is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

### ***Australian regulatory information***

According to the Globally Harmonised System (GHS) of classification, helium is a non-flammable non-toxic gas 2.2 and requires the following label:



### ***International regulations***

#### *New Zealand (NZ) and United Kingdom (UK)*

The ACCC is aware of some efforts to address the misuse of helium in NZ and the UK. However, no jurisdictions appear to have been able to find an appropriate solution or achieve any regulatory change.

- Australia New Zealand Industrial Gas Association (ANZIGA) members have provided informal advice that approaches considered in NZ and the UK have included the use of 'Heliox' (79% helium + 21% oxygen) as an inflation gas for balloons and the inclusion of aversives. The NZ Ministry of Business, Innovation & Employment consulted their local gas industry about the 'Heliox' approach in March-April 2016.
- Advice from ANZIGA is that in NZ there was concern about flammability issues with balloons inflated with 'Heliox', especially as helium is likely to leach from a balloon faster than oxygen, leaving the highly flammable oxygen in the balloon.

#### *United States of America (USA)*

According to Title 21: Food and Drugs:

- [Part 582.1355](#), helium is "generally recognised as safe when used in accordance with good manufacturing or feeding practice".
- [Part 184—direct food substances affirmed as generally recognized as safe](#), helium must be of purity suitable for its intended use and when used in food, helium has no limitations other than current good manufacturing practice.

[Part 201 Labelling](#), a warning statement must be included on medical gas canisters containing helium indicating that the administration of the gas or gas combination may be hazardous or contraindicated; and that the gas or gas combination should only be used by or under the supervision of a licenced practitioner who is experienced in the use and administration and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration.



### §201.328 Labeling of medical gas containers.

(a) *Portable cryogenic medical gas containers.* For the purposes of this section a "portable cryogenic medical gas container" is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at §868.5655 of this chapter).

(1) Each portable cryogenic medical gas container must be conspicuously marked with a 360° wraparound label identifying its contents. Such label must meet the requirements of §211.94(e)(2) of this chapter and the following additional requirements.

(i) If the container holds a single gas, the name of the gas held in the container must be printed on the label in one of the following ways:

(A) Using lettering that appears in the color designated for the gas in paragraph (c) of this section and that is printed against a white background, or

(B) Using lettering that appears in white against a background that is painted in the color for the gas designated in paragraph (c) of this section.

(ii) The lettering for the name of the gas on the label must be at least 2 inches high.

(iii) The name of the gas must be printed continuously around the label and be capable of being read around the entire container.

(iv) The label must be on the sidewall of the container, as close to the top of the container as possible but below the top weld seam.

(v) A portable cryogenic medical gas container may only be colored in the color or colors designated in paragraph (c) of this section if the gas or gases held within the container correspond to that color or those colors.

(2) A label on the container (either the 360° wraparound label required in paragraph (a)(1) of this section or a separate label) must include, in conspicuous lettering, the phrase "For Medical Use", "Medical Gas," or some similar phrase that indicates the gas is for medical use.

(b) *High-pressure medical gas cylinders.* Each high-pressure medical gas cylinder must be colored on the shoulder portion of the cylinder in the color or colors designated in paragraph (c) of this section. The color or colors must be visible when viewed from the top of cylinder.


(c) *Medical gas colors.* The colors required to identify medical gases under paragraph (a) and (b) of this section are:


Medical gas	Color
Medical Air	Yellow.
Carbon Dioxide	Gray.
Helium	Brown.
Nitrogen	Black.
Nitrous Oxide	Blue.
Oxygen	Green.
Mixture or Blend	Colors corresponding to each component gas.

[81 FR 81696, Nov. 18, 2016]

*European Union (EU) (ECHA):*

The hazard classification and labelling of helium is 'Warning' in the EU:

**Hazard classification & labelling** 



*Warning!* According to the classification provided by companies to ECHA in **CLP notifications** this substance contains gas under pressure and may explode if heated and contains refrigerated gas and may cause cryogenic burns or injury.

### **Substance summary**

Helium gas is a simple asphyxiant that is insoluble in body tissues.

**Table 2.1.1: Chemical properties of helium**

Property	Helium
CAS number	7440-59-7
Chemical structure	He
Chemical name	Helium
Atomic weight	$A_r(\text{He}) \approx 4.003$
Colour	Colourless
Odour	Odourless
Taste	Tasteless
Reactivity	Inert (Noble) gas
Flammability and explosivity	Not combustible; If heated in a sealed vessel, may expand to rupture container

*Acute toxicity*

Lethal doses or concentrations not established.

*Skin and eye irritation*

Not an eye or skin irritant and non-corrosive.

*Sensitization*

No sensitisation effects.

*Repeat-dose toxicity*

N/A.

*Carcinogenicity and genotoxicity*

Not mutagenic, carcinogenic or a teratogen.

*Reproduction and developmental toxicity*

Not a reproductive toxicant.

*Commercial and industrial uses:*

- Manufacture of various materials (e.g. semi-conducting materials, optical glass fibres);
- Inert gas shield in gas-tungsten arc welding (GTAW);
- In gas mixtures in Geiger counters, lasers;

- In breathing gas mixtures for commercial deep diving or technical diving e.g. in 'Heliox' or 'Trimix';
- Creation of an inert atmosphere for growth of crystals and in supersonic wind tunnels;
- Coolant in high-temperature nuclear reactors;
- Inert gas diluent;
- Carrier gas in gas-liquid and gas-solid chromatography; and
- Lifting gas in airships or dirigible balloons.

*Medical uses:*

- Supportive treatment in patients with respiratory obstruction (in combination with other gases);
- Liquid cryogen in MRI machines; and
- Rare use in gas mixtures for lung inflation during airway surgery or as a diluent in certain anaesthetic gas mixtures.

*Domestic uses:*

- Inflation of 'floating' party or decorative balloons and novelty items.

*Misuses:*

- Squeaky or cartoon voice 'party trick';
- Possible short term euphoric 'high' through deliberate inhalation ('huffing'); and
- Suicide.

***Section 52(E) criteria of the Therapeutic Goods Act 1989***

*(a) Risks and benefits associated with the use of a substance*

**Social benefit of continued domestic supply of helium:**

- Helium gas in a domestic or household setting is legitimately used for inflation of balloons or similar novelty items, such as 'air swimmers'. These balloons are used as decorations, for amusement and as gifts. The balloons are generally made of light mylar or 'foil'. The balloons float in air due to the weight of the helium and the balloon being less than the air that it displaces. Normal thin rubber balloons can also be inflated with helium gas, but they are heavier and deflate much faster than mylar balloons.
- Domestic use of helium gas in balloons as decoration or as a gift has social benefit, but could be considered non-essential. This type of benefit is difficult to quantify or value.
- This application proposes the addition of an aversive to helium gas canisters or cylinders sold or hired for domestic use. The use of the gas by householders for balloon inflation is not affected by the addition of an aversive to the helium gas canister/cylinder, so this social benefit continues.

**Risks of continued domestic supply of helium**

- Uses of helium in the domestic or household setting other than for balloon inflation are considered misuses and are dangerous to health. These misuses involve the deliberate inhalation of helium for suicide, 'huffing' and a squeaky voice party trick.

- As a simple asphyxiant, inhalation of helium can result in rapid hypoxia or death. Death may be deliberate (suicide) or accidental (as a result of over-inhalation) while ‘huffing’ or trying to achieve a squeaky voice for fun. Symptoms of hypoxia can include light-headedness or dizziness, which can also result in falls and injuries.
- Information about the demographic of people who commit suicide using helium asphyxiation was not included in the data provided by the NCIS. The literature does not closely define the type of person that may choose to commit suicide by this method, but they are likely to include vulnerable consumers. Some researchers have suggested that mental illness is a commonality, but this is not likely to be unique to people who consider helium asphyxiation, as opposed to other methods of suicide. Some researchers have identified features of people choosing to commit suicide by helium asphyxiation. People committing suicide by helium asphyxiation were more likely to be younger (Howard *et al.*, 2011, Gunnell *et al.*, 2015a, Chang *et al.*, 2016), more affluent (Gunnell *et al.*, 2015a), have a psychiatric disorder (Howard *et al.*, 2011), have financial problems (Chang *et al.*, 2016) and a history of substance abuse (Howard *et al.*, 2011). These characteristics are not inconsistent with the details of cases that the ACCC has been alerted to by the Victorian Coroner.
- The literature indicates that helium asphyxiation suicides are often preceded by a period of research on the internet (Gunnell *et al.*, 2015a, Chang *et al.*, 2016). Gunnell *et al.*, (2015b) did not find a generalised increase in internet searching for information about helium for suicide (2004-2014), but increased searching was documented following news coverage of helium suicides by celebrities. Around one third of links from Google searches for “suicide” mentioned helium (Gunnell *et al.*, 2015b).
- This application proposes that domestic users of helium should only be able to access helium gas that contains an aversive. This will not reduce the social utility of helium gas in the domestic or household setting, but it may reduce the misuse of the gas in this setting.

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

#### **Domestic and household use:**

- Helium gas is widely and properly used in a domestic or household setting for the inflation of party balloons and similar novelty items e.g. ‘air swimmers’. Consumers may purchase balloons pre-inflated with helium from commercial outlets, such as party supplies stores or party hire businesses. Consumers can also purchase or hire kits that allow them to inflate the balloons themselves. It is unknown how long helium gas cylinders have been available to the public.

Helium balloon inflation kits can be purchased without restriction from retail stores. Helium balloon inflation kits for sale or hire to consumers always include a helium gas canister with fittings. Helium canisters are small non-refillable and disposable. Most kits also include a selection of balloons and trimmings; some require a consumer to separately purchase balloons for use with the canister.

#### **Commercial and industrial use**

- Helium gas has a range of commercial and industrial uses, including in gas tungsten-arc welding (GTAW), manufacturing and in certain medical/scientific equipment. Helium is used in commercial deep diving and technical diving in combination with oxygen (‘Heliox’) and sometimes also nitrogen (‘Trimix’). It is used very rarely in medical or surgical practice, and this is generally in combination with other gases.
- This application is intended to prevent the supply of helium without an aversive to consumers. It is not intended to affect the supply of helium gas to existing commercial or industrial users and proposes that helium for commercial or industrial use continues to be supplied without an aversive.

- Party supplies stores and party hire outlets would continue to sell balloons inflated to order with helium from cylinders without an aversive, but would not be permitted to sell or hire helium gas cylinders or balloon inflation kits to consumers without an aversive.

*(c) Toxicity and safety of the substance*

Helium gas is non-toxic. It is a colourless, odourless and tasteless gas and is a simple asphyxiant.

**Simple asphyxiants:**

- The normal level of oxygen in fresh air is about 21 per cent. Oxygen concentrations below 16 per cent are dangerous to human health. Early signs of oxygen deprivation include dizziness and light-headedness. With continued exposure to a low-oxygen atmosphere, unconsciousness follows very quickly. Oxygen concentrations below 10 per cent cause rapid brain damage. Oxygen levels below 6 per cent cause unconsciousness in less than one minute (1-2 breaths), followed by death a few minutes later.
- Simple asphyxiants displace oxygen in the lungs, causing reduced alveolar partial pressure of oxygen and, as a consequence, hypoxemia. Other gases classified as simple asphyxiants include argon, nitrogen, carbon dioxide, sulfur hexafluoride, hydrogen sulphide and gaseous hydrocarbons such as methane, ethane, propane and butane.
- Because helium is a simple asphyxiant, there are no occupational exposure limits established for the gas in Australia or overseas. Essential use of helium in the workplace requires engineering controls and personal protective equipment to ensure an adequate oxygen supply to the worker. All Safety Data Sheets (SDSs) for helium gas note the potential for rapid asphyxiation from exposure to helium.
- The Globally Harmonised System of Classification and Labelling of Chemicals (GHS) requires labelling of gases under pressure with standard pictograms and hazard statements (Pictogram GHS04 and 'Contains gas under pressure; may explode if heated.').
- A Safety Advice Bulletin<sup>48</sup> published by the Australia New Zealand Industrial Gas Association notes that "The 'fun' to be found in the squeaky voice helium trick is far from funny when people, often youngsters, die trying this. It does not take many breaths of helium to fall unconscious and die this way."

*(d) Dosage, formulation, labelling, packaging and presentation of a substance*

**Formulation:**

- The ACCC proposes that all helium gas canisters or cylinders sold or hired to consumers for domestic or household use i.e. for inflation of balloons, should include an aversive. This will reduce the attractiveness of the gas as a suicide agent and should also deter many people attempting suicide from completing the act.
- It is not proposed to require an aversive to be added to helium gas sold for commercial or industrial purposes. Party supply stores (commercial use) could continue to sell pre-inflated helium balloons using helium without an aversive.
- The inclusion of an aversive in helium sold to consumers will also reduce the likelihood of accidental deaths from inhalation of helium from canisters or cylinders and from balloons that the consumer has inflated themselves.

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<sup>48</sup> [ANZIGA Safety Advice No.22 \(Document No. 142-022 \(version 2\) The Dangers of Industrial Gas Abuse](#)

- Some other gaseous products have included aversives to discourage the inhalation (or 'huffing') of the propellants in these products. Examples include gaseous cleaners for electronics, computers and photographic equipment.

#### **Packaging and presentation:**

- Helium gas canisters in balloon inflation kits are purposefully designed to be very simple to use (see image below). A balloon is attached to a nozzle and a valve is opened to allow gas to flow from the canister. The nozzle is pressed down or lifted upwards, causing the gas to flow under pressure from the canister into the balloon. To stop the flow of gas, the pressure on the nozzle is released.



**Figure 2.1.1: Simple valve and nozzle fixings on helium balloon canister**

- Separate to this scheduling proposal, the ACCC is consulting with the bottled gas industry about possible amendments to the simple valve and nozzle presentation on helium canisters available to the public. The aim is to alter the presentation of the canister to make the gas more difficult to remove from the canister. Changes may include the need to repeatedly depress a part to keep the gas flowing. These changes will mean that someone impaired with alcohol or other drugs e.g. sedatives, will be less able to complete the suicide act and will also stop the flow of gas once the user is unconscious. These changes may also reduce the likelihood of children being able to release helium from the canister, given that these products are in the home.
- The ACCC notes that imported helium canisters do not appear to be subject to Australian Standards, so the presentation of these products may need to be regulated through an amendment to the *Poisons Standard*. This will require a supplementary application to amend the *Poisons Standard*.

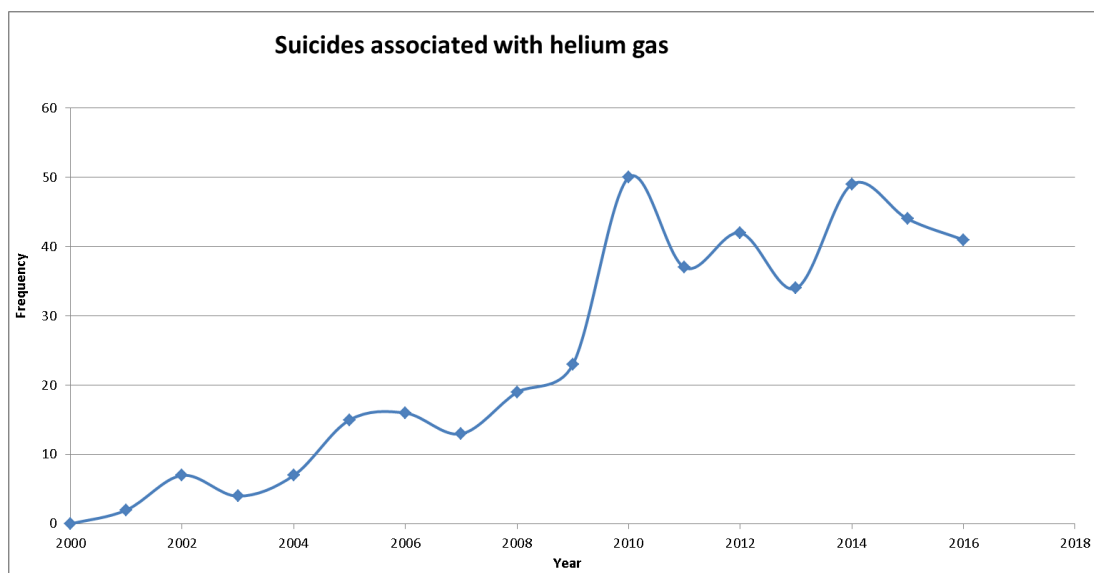
#### *(e) Potential for misuse/abuse of the substance*

#### **Suicide:**

- The ACCC requested data from the National Coronial Information System (NCIS) on the frequency of use of helium gas for suicide from 1 July 2000 to 31 December 2016. Additional information was extracted from case notes in relation to state/territory location of the suicide, whether the helium canister or cylinder was purchased or hired (where known) and the source of the helium (where known). The NCIS data was expressly provided for the purpose of the ACCC making an application to the ACCS to amend the *Poisons Standard*.
- Trends in suicide by helium asphyxiation



- No suicides by helium asphyxiation were recorded in the NCIS for 2000. Actual or extrapolated<sup>49</sup> annual numbers of helium suicides in Australia for each year from 2000 to 2016 are shown in the figure below.
- There have been an estimated 400 suicides using helium gas between 2000 and 2016 (an average of about 24 each year). The number of cases gradually increased between 2000 and 2009, but more than doubled in 2009-10, increasing from 23 to 50 cases each year. The higher number of helium asphyxiation suicides per year has been relatively steady since 2010, at about 45 cases per year (figure below).



**Figure 2.1.2: Annual Australian suicides using helium asphyxiation**

- The NCIS data is consistent with Australian and overseas studies of the rates of helium asphyxiation suicide. Increasing helium asphyxiation rates since the early 2000s have been documented in Australia and Sweden (Austin *et al.*, 2011), Hong Kong (Chang *et al.*, 2016), the Netherlands (van den Hondel *et al.*, 2016) and the USA (Hassamal *et al.*, 2015; Azrael *et al.*, 2016).
- The NCIS data was examined for geographical trends by calculating a rate of helium asphyxiation suicide for each state and territory over the period 2000 to 2016 (Table below).
- In over 70 per cent of investigated cases, the source of helium used to commit suicide is unknown. Seventy six per cent of known sources of helium are party goods suppliers (73 cases), followed by 14 per cent from industrial gas suppliers (13 cases). Other minor sources include online, voluntary euthanasia organisations and suppliers of goods for building, lighting, agriculture, diving and pumping.
- The method of acquiring helium cylinders and canisters (where known) was split roughly evenly between purchasing and hiring.
- Attractiveness of helium as a suicide agent
  - Asphyxiation with inert gases, including helium, is widely publicised as certain, simple, quick, painless and non-disfiguring. The materials required are all familiar to everyone and freely available without any restriction, age limits or cooling off periods.

<sup>49</sup> Where there were open (investigations incomplete) cases for any given year, the number of expected cases was estimated by extrapolating from the frequency and the number of closed cases to give a predicted frequency for that year. For example, if there were 25 helium suicides recorded, but only 50 per cent of the cases were closed, the total for that year would be estimated at 50 cases. This method of extrapolation was used for data from 2014, 2015 and 2016.



- Information about how to commit suicide using these materials is accessible on the internet, videos and in publications. ‘Right to die’ advocates have promoted the right to voluntary euthanasia (“self-deliverance”) in terminally ill patients and otherwise healthy elderly people. Voluntary euthanasia using various drugs, devices and asphyxiants is publicised through books, documentaries, meetings and the internet. Several books describing the use of these methods are banned in Australia.
- Austin *et al.*, (2011) quotes Dr Richard McDonald speaking at the 13th National Hemlock Biennial Conference in San Diego USA in 2003: “...we have had a shift to techniques using plastic bags and helium. That, remarkably, has become an acceptable method of hastening death... It is a very speedy process and has never failed in our program.”
- Suicide by helium asphyxiation is not easily detectable through standard physical, pathological or toxicological examination after death, which is attractive to some people considering suicide. Suicide by helium asphyxiation leaves an intact corpse without disfiguration. Typically, helium suicide is detected only through the presence of equipment at the scene or, in rare cases, by ligature marks where a plastic bag fastened on the neck has been removed. If equipment is removed before an investigation of the death, the cause of death may not be classified as a suicide by helium asphyxiation. This could occur in the case of an assisted suicide or by loved ones wishing to avoid a finding of death by suicide due to social stigma or cultural concerns. This indicates that the documented frequency of suicide by helium is likely to be an underestimate. In addition, given the illegality of assisted suicide, a method that leaves little or no evidence once equipment is removed may be ideal for a pre-arranged suicide.

#### **Deliberate inhalation of helium gas for a squeaky voice effect:**

- It is common for both adults and children to inhale gas from helium balloons at parties to achieve the squeaky/cartoon voice effect. Because this party trick is so common and sounds funny, helium gas has a reputation as being a ‘harmless’ and ‘fun’ gas to inhale.
- This squeaky voice effect is due to the lower density of helium (compared to nitrogen, the main component of air). Sound travels faster through the helium in the vocal tract, altering the timbre of the voice and making it sound squeakier.
- People inhaling deeply from a balloon of helium gas may experience dizziness or light-headedness. This may result in falls and injuries.
- Another method of inhaling helium is directly from the cylinder or canister. This is extremely dangerous as the gas under pressure may rupture the lungs or cause an air embolism. Contact with liquid helium or helium directly from a pressurised cylinder or canister may also cause an injury similar to severe frost bite in the mouth, throat and lungs, which can be fatal.

#### **Deliberate inhalation of helium gas for short term ‘high’:**

- In a 2012 study of at-risk adolescents, Whitt *et al.*, (2012) reported that 11.5 per cent of the 723 study subjects had inhaled helium gas with the intention of getting ‘high’ – a practice known as ‘huffing’. In this study, over a third of the users claimed to have experienced a ‘high’ from this activity. Although helium does not have any psychoactive effects, users may experience light-headedness, dizziness or euphoria caused by short-term oxygen deprivation. These symptoms can result in falls or other accidents, leading to injury.

*(f) Any other matter that may be relevant to the scheduling of a substance*

#### **The bottled gas industry:**

- The dominant companies in Australian gas production are made up by two companies (10.2 per cent market share), with smaller companies making up the remainder. The contribution of helium sales to the industrial bottled gas producers’ profit is unknown. Australian producers are required to comply with Australian Standards relating to bottled gas.

- There are also a large number of disposable non-refillable helium canisters or balloon inflation kits imported into Australia. These products are freely sold in party supply shops and discount department stores. These products are not required to comply with Australian Standards.
- The bottled gas industry is subject to several regulatory frameworks. Aspects of the bottled gas industry are regulated by the dangerous goods transportation legislation, the industrial chemical framework, as chemicals used in workplaces and with links to the gas appliance safety system.
- There are many voluntary Australian Standards that apply to bottled gas, including:
  - AS 2030.1-2009 Gas cylinders general requirement
  - AS 2473.2:2015 Valves for compressed gas cylinders. Outlet connections (threaded) and stem (inlet) threads
  - AS 4332-2004 (R2016) and AS 4332-2004/ (R2016)Amdt1-2005 The storage and handling of gases in cylinders
  - AS 3840.1-1998(R2016) Pressure regulators for use with medical gases. Pressure regulators and pressure regulators with flow-metering devices
  - AS 4484:2016 Gas cylinders for industrial, scientific, medical and refrigerant use - Labelling and colour coding
- Several additional AS, AS/NZ and ISO Standards apply to medical gases and the construction of gas cylinders.
- 70. The bottled gas industry is aware of the dangers of inhaling helium (ANZIGA representatives, pers comm). In 2014, bottled gas companies ELGAS and BOC launched a safety advertisement warning of the danger of inhaling helium: [Inhaling gas from helium balloons no laughing matter, it can kill.](#)

#### **International approaches to prevention of helium misuse**

- The ACCC is aware of some efforts to address the misuse of helium in New Zealand and the UK. However, no jurisdictions appear to have been able find an appropriate solution or achieve regulatory change.
- ANZIGA members have provided informal advice that approaches considered in New Zealand and the UK have included the use of 'Heliox' (79% helium + 21% oxygen) as an inflation gas for balloons and the inclusion of aversives. The New Zealand Ministry of Business, Innovation & Employment consulted their local gas industry about the 'Heliox' approach in March-April 2016.
- Advice from ANZIGA is that in New Zealand there was concern about flammability issues with balloons inflated with 'Heliox', especially as helium is likely to leach from a balloon faster than oxygen, leaving the highly flammable oxygen in the balloon.
- The ACCC is continuing to investigate the outcomes of the New Zealand and UK proposals and consultations.

#### **Data gaps**

- The ACCC has been unable to find information about the feasibility of the addition of an aversive to helium gas. Some aerosol "compressed air" products used for cleaning electronic and photographic equipment contain an aversive to prevent 'huffing' of the product. However, no information is available about the identity or concentration of the aversive in these products. The ACCC is aware that progress of this proposal will require information from the bottled gas industry and this is being sought.

- In addition, the ACCC has not been able to find information about the extent of the aversion effect that would be required to prevent inhalation of helium when supplied containing an aversive. The bottled gas industry may have conducted but not published the relevant research.

### **Consideration of Scheduling Policy Framework (SPF) criteria**

The public health policy framework includes a system for safe access to chemicals and safe use of these chemicals through the chemical scheduling arrangements, including any necessary restrictions on supply and requirement of appropriate labelling. Chemical scheduling considerations include:

- the chemical's toxicity;
- purpose and need for access;
- potential for abuse or misuse;
- safe use practice, packaging and labelling; and
- the need for any specialist knowledge or equipment for the safe and effective use of the chemical.

#### **Schedule 9: Prohibited substances**

- The substance is not included in United Nations Conventions on narcotic drugs or psychotropic substances.
- The substance does not require restriction to use in medical and scientific research. The substance has a long history of legitimate and safe use in domestic, commercial, industrial and medical situations.
- The substance does not present a risk of dependency or abuse.
- The substance is legitimately supplied for household/domestic use for the inflation of balloons. The substance presents some risk of misuse (suicide). The misuse is not extensive and does not warrant stringent controls on supply from Schedule 9, given the social benefit from the legitimate use of the substance for inflation of balloons.

*Schedule 9 is not suitable.*

#### **Schedule 7: Dangerous Poison**

- Helium is non-toxic.
- Helium is of a high health hazard and may cause death if inhaled.
- Special precautions are required in the manufacturing, handling and use of helium. An atmosphere containing sufficient oxygen to sustain life must be maintained at all times, as helium is a simple asphyxiant. There are no workplace exposure standards for helium and the Hazardous Chemical Information System (HCIS ) notes that it is an asphyxiant.
- Helium has a high potential for causing harm at relatively low exposure and without warning of the asphyxiation effect. The substance is colourless, odourless and tasteless. Asphyxiation by this substance occurs very quickly and rescue is unlikely.

Suitable when the substance is used in a commercial or industrial setting and adequate safety precautions and training are in place.

The ACCC notes that application of Appendix J to Schedule 7 may add further controls for commercial and industrial suppliers and users of helium gas. However, adoption of Appendix J varies between States and Territories and there is currently no reason to expect that supplies of helium without an aversive would be illicitly supplied to consumers.

#### **Schedule 6: Poison**

- The substance is non-toxic.
- The substance is an asphyxiant.
- The proposal is for the substance to be required to include an aversive when supplied for household or domestic use. The aversive e.g. mercaptan, will have an aversion effect.
- Apart from the risk of asphyxiation, the substance does not present a health hazard. The inclusion of an aversive should reduce the risk of asphyxiation through deliberate inhalation.
- Foreseeable harm to users is not likely to be reduced by distinctive packaging, strong label warnings or extensive safety directions. Inhalation of the substance causing fatalities is normally deliberate.
- Changes to the packaging and presentation of the substance (specifically the simple nozzle/valve arrangement), with or without an aversive, may make the substance less accessible to both adults and children. This may reduce fatalities due to deliberate inhalation of the substance.
- Without an added aversive, the substance has a high potential to cause harm at low exposure. With an added aversive the potential for causing harm is reduced (through aversion), but not eliminated.

*Suitable when the substance has an added aversive and is supplied for household or domestic use.*

### Schedule 5: Caution

The proposal is for the substance to be required to include an aversive when supplied for household or domestic use. The aversive e.g. a mercaptan, will have an aversion effect.

- The substance is non-toxic and is not corrosive or sensitising.
- The substance is an asphyxiant. An asphyxiant is not a low health hazard, even with the addition of an aversive. The substance with an aversive may still be inhaled in sufficient quantity to cause a fatality.
- The substance is an asphyxiant. Adverse effects from sustained inhalation are not minor as fatality is likely. Very short term exposure is likely to have minor adverse effects, including dizziness, light-headedness and potential injuries from falls.
- Risk of injury from normal handling, storage and use could be mitigated through labelling and appropriate packaging. Labelling and packaging will not reduce misuse or attempted misuse of the substance if an aversive is not included. Inclusion of an aversive and appropriate labelling may reduce attempted misuse of the substance.
- Without an added aversive, the substance has a high potential to cause harm at low exposure. With an added aversive the potential for causing harm is reduced (through aversion), but not eliminated.

*Suitable when the substance has an added aversive and is supplied for household or domestic use.*

### Appendix B: Exempt from scheduling

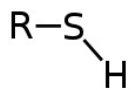
*Not suitable as helium gas meets factors for Schedule 7 (DANGEROUS POISON) for industrial and commercial uses of helium and Schedule 6 (POISON) or Schedule 5 (CAUTION) for domestic and household use when an aversive is included to prevent deliberate inhalation that results in fatalities.*

Consideration of the Scheduling Factors indicates that helium (with an aversive) for household or domestic use could be included in either Schedule 6 or Schedule 5 of the *Poisons Standard*. The ACCC recommends that the substance is included in Schedule 6, given the rapidity of the asphyxiation effect, even if an aversive is included.

## *Aversives*

### *Mercaptans*

Mercaptans (thiols) are organosulfur compounds that contain a carbon-bonded sulfhydryl group:



**Figure 2.1.3: Chemical structure of mercaptans, where R can be an alkane, alkene or other carbon-containing moiety.**

**Table 2.1.2: Properties of the mercaptans (Committee on Acute Exposures Guideline (2013))**

Mercaptan	Descriptors	Acute Exposure Guideline Levels (AEG <sup>L50</sup> ) for 10 minute exposure	Odour intensity or awareness (LOA <sup>51</sup> ) detection thresholds and descriptors	4 hour inhalation LC <sub>50</sub> (ppm) (rats/mice)	Effects
methyl mercaptan CH <sub>4</sub> S	Strong odour, garlic-like, rotten cabbage, bad breath	AEGL-1 = no recommendation AEGL-2 = 40 ppm (80 mg/m <sup>3</sup> ) AEGL-3 = 120 ppm (240 mg/m <sup>3</sup> )	LOA = 0.0019 ppm Detection threshold = 0.041 ppm Strong intensity = 110 ppm	675 / 1667	CNS depression, affects respiratory centre, ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, vomiting.
ethyl mercaptan C <sub>2</sub> H <sub>6</sub> S	Penetrating, persistent odour, garlic/leek-like, skunk-like, decaying cabbage	AEGL-1 = 1 ppm (2.5 mg/m <sup>3</sup> ) AEGL-2 = 150 ppm (380 mg/m <sup>3</sup> ) AEGL-3 = 450 ppm (1100 mg/m <sup>3</sup> )	LOA = 1.4 x 10 <sup>-4</sup> ppm Detection threshold = 2.6-9.7 x 10 <sup>-4</sup> ppm Strong = 21-97 ppm	4420 / 2770	CNS depression, affects respiratory centre, ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea, vomiting.
phenyl mercaptan C <sub>6</sub> H <sub>6</sub> S	Disagreeable, penetrating and repulsive odour, garlic-like	AEGL-1 = no recommendation AEGL-2 = 1 ppm (4.5 mg/m <sup>3</sup> ) AEGL-3 = 3 ppm (14 mg/m <sup>3</sup> )	Detection threshold = 0.00025 ppm Strong = 38 ppm	33 / 28	Ocular and mucous membrane irritation, headache, dizziness, staggering gait, nausea and vomiting.
<i>tert</i> -octyl mercaptan C <sub>8</sub> H <sub>18</sub> S	Disagreeable	AEGL-1 = no recommendation AEGL-2 = 0.77 ppm (4.6 mg/m <sup>3</sup> ) AEGL-3 = 2.3 ppm (14 mg/m <sup>3</sup> )	-	51 / 47 (both males only)	Moderately irritating to the eyes, may cause headache, nausea, vomiting and CNS effects resulting in dizziness, convulsions, unconsciousness and respiratory depression

<sup>50</sup> AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. The effects are not disabling and are transient and reversible upon cessation of exposure. AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death

<sup>51</sup> Concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odour intensity and about 10% of the population will experience a strong odour intensity

Many mercaptans have strong odours and are dominant contributors to repulsive smells including garlic, rotten eggs, rotten cabbage, skunk spray and certain chemical faults in wines etc. Mercaptans (generally methyl mercaptan and ethyl mercaptan) and sulfides are added to natural gas supplies and other odourless gases so that consumers can be aware of the gas.

Inhalational toxicity levels and ability of people to detect mercaptans vary. Phenyl mercaptan and tert-octyl mercaptan are both highly toxic than the lower molecular weight mercaptans, methyl mercaptan and ethyl mercaptan. Compared to methyl mercaptan, ethyl mercaptan has lower inhalational toxicity in rats and mice as well as a lower detection threshold.

Ethyl mercaptan appears to be the most suitable mercaptan candidate for inclusion in helium gas as an aversive.

The ACCC requests the Scheduling Delegate commission expert advice about the suitability of the mercaptans (and potentially other aversives) as suitable candidates for inclusion in helium gas for consumer or domestic use.

### ***Pre-Meeting Public Submissions***

Eight (8) public submissions were received for helium, one (1) in support and seven (7) opposed.

#### *Main points in support:*

- Data from the National Coronial Information System (NCIS) shows an increase in deaths with helium listed as the cause of death. All of these deaths were intentional suicides in individuals ranging in age from 16 years to 94 years.
- Availability of helium for purchase online in large quantities makes this an attractive, easy, relatively inexpensive and very efficient method of suicide.
- Online resources supporting euthanasia run workshops and sell adaptors to facilitate the use of helium for asphyxiation.
- Additionally, the inclusion of an aversive in canisters of helium being sold or hired to consumers should make exposure to excessive quantities of helium more difficult and unpleasant.

#### *Main points opposed:*

- The occupational work health and safety of people who work with helium regularly and of the general public who might inhale the new gas mixture is of great concern. Rupture of a balloon filled with helium, or the leaching of helium and aversive through the latex membrane of a balloon would allow the undesirable release of the aversive into the work, home and event areas and may result in future medical issues.
- There are many uses of helium that are essential for society, for example in MRI scanners.
- Helium is only dangerous if deliberately misused.
- The inclusion of an aversive would be impractical with positive environmental policies. These policies outline the proper disposal of helium balloons, which includes popping the balloon prior to disposal. Popping a balloon with such an aversive would be unpleasant and would therefore reduce the implementation of environmentally conscience disposal practices.
- The use of an aversive has further been discussed by international authorities and organisations to some length but has never been implemented as the use of an aversive could potentially endanger or destroy the balloon industry.
- The imposition of Schedule 7 requirements on helium will make small business operation very costly.



- Helium does not meet the criteria for scheduling as outlined in the Scheduling Policy Framework.
- The release of helium or other asphyxiant gases straight from its packaging is not the path taken to commit suicide. It is the additional intentional and conscious step by the end user to restrict their atmosphere through a piped direct application method (regulator, tubing and face mask) that is used to displace oxygen. Helium, when used as intended, either for industrial or medical uses, poses little risk to the user.
- There is the potential for all oxygen displacing gases to be inappropriately used. Inert gases such as nitrogen, argon and carbon dioxide have similar asphyxiation hazards. The scheduling of one substance is unlikely to solve the problem, but will shift the focus to another.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACCS-ACMS advice to the delegates***

The committee recommended that helium does not require scheduling.

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

The reasons for the recommendation comprised the following:

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

- The benefits of helium are that it has many legitimate uses, most of which are non-balloon uses, e.g. industrial, scientific and medical uses.
- The risks for helium do not exist unless it is deliberately inhaled (resulting in oxygen deprivation, leading to asphyxiation); helium is otherwise safe.

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

- Helium has a small number of therapeutic uses as part of gas mixtures.
- Helium has commercial, industrial and medical uses.
- A small amount of helium is also used in domestic situations, primarily for balloons and similar items.

c) *the toxicity of a substance:*

- Helium is an inert, non-toxic gas.
- Correct and legitimate use of helium does not meet the scheduling criteria (SPF 2015).

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

- Nil.

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

- Helium may be deliberately misused for the purpose of causing asphyxiation but use does not result in dependence or addiction.

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

- The addition of an aversive may make the gas more dangerous and the evidence that this would lead to aversion is not there.

- The ACCC should continue to work with the helium industry to reduce risks such as the proposal to modify valves and nozzles for cylinders that increase the difficulty of completing the suicide act. These changes will also reduce the likelihood of children being able to release helium from a canister.

### ***Delegates' considerations***

The delegates considered the following in regards to this proposal:

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

### ***Delegates' interim decision***

The delegate's interim decision is not to schedule helium.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

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

- The benefits of helium are that it has many legitimate uses, most of which are non-balloon uses, e.g. industrial, scientific and medical uses.
- The risks for helium do not exist unless it is deliberately inhaled (resulting in oxygen deprivation, leading to asphyxiation); helium is otherwise safe.

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

- Helium has a small number of therapeutic uses as part of gas mixtures.
- Helium has commercial, industrial and medical uses.
- A small amount of helium is also used in domestic situations, primarily for balloons and similar items.

c) *the toxicity of a substance:*

- Helium is an inert, non-toxic gas.
- Correct and legitimate use of helium does not meet the scheduling criteria (SPF 2015).

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

- Nil.

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

- Helium may be deliberately misused for the purpose of causing asphyxiation but use does not result in dependence or addiction.

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

- The addition of an aversive may make the gas more dangerous and the evidence that this would lead to aversion is not there.
- The ACCC should continue to work with the helium industry to reduce risks such as the proposal to modify valves and nozzles for cylinders that increase the difficulty of completing the suicide act. These changes will also reduce the likelihood of children being able to release helium from a canister.

## 2.2 Salts of Boric Acid

### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the current entry for boric acid in Schedule 5, to remove “*excluding its salts*”, so salts of boric acid are captured by scheduling in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

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

#### **Schedule 5 – Amend Entry**

BORIC ACID (~~excluding its salts~~) and BORAX **except:**

- a) when included in Schedule 4;
- b) in preparations, other than insect baits, containing 1 per cent or less of boron; or
- c) in hand cleaning preparations.

The applicant’s reasons for the request are:

- Data from animals indicate that boric acid and its salts are reproductive and developmental toxins.
- Boric acid and its salts are reported to be used in cosmetic and domestic products overseas and are therefore, likely to be used in similar products in Australia.
- Boric acid and its salts have international restrictions on their use.

### *Current scheduling status*

The salts of boric acid are captured by the Schedule 4 entry for BORON in the current [Poisons Standard](#) as follows:

#### **Schedule 4**

BORON, including boric acid and borax, for human therapeutic use **except:**

- a) in preparations for internal use containing 6 mg or less of boron per recommended daily dose;
- b) in preparations for dermal use containing 0.35 per cent or less of boron, which are not for paediatric or antifungal use; or

- c) when present as an excipient.

Boric acid is included in Schedule 5 and Appendix E, Part 2. However, salts of boric acid are specifically excluded as follows:

### **Schedule 5**

BORIC ACID (excluding its salts) and BORAX **except**:

- a) when included in Schedule 4;
- b) in preparations, other than insect baits, containing 1 per cent or less of boron; or
- c) in hand cleaning preparations.

### **Appendix E, Part 2**

BORIC ACID

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)).

### **Index**

#### **BORON**

cross reference: BORATES, BORAX, BORIC ACID, BORON COMPOUNDS

Schedule 4

### ***Scheduling history***

The scheduling history for boron compounds dates back to July 1968. The most recent scheduling considerations are highlighted below.

#### *May and August 2001 National Drugs and Poisons Schedule Committee (NDPSC)*

The May and August 2001 NDPSC Meetings agreed to revise the boron Schedule 4 entry to exempt a daily oral dose of 3 mg and to exempt dermal preparations containing 0.35 per cent or less to harmonise with the New Zealand (NZ) classification for dermal use. However, the committee did not agree to harmonise on other use patterns. This outcome was referred to NZ's Medicines Classification Committee (MCC) for consideration.

#### *February 2006 National Drugs and Poisons Schedule Committee (NDPSC)*

The February 2006 NDPSC Meeting:

- Noted that NZ had toxicity concerns regarding the use of high strength boron for nappy rash in babies under occlusive conditions.
- Noted that NZ products only contained boric acid and that boron was not listed as an ingredient in medicines. In contrast, registered ingredients for Australian therapeutic products include either boron or boric acid. A Member also noted that the boron scheduling excluded excipients and that this may need to be reviewed on the basis of the substance's toxicity.
- Recommended that NZ consider harmonising with the scheduling of boron and that MCC consider submitting a proposal to the NDPSC regarding appropriate nomenclature for harmonisation.

### *June 2007 National Drugs and Poisons Schedule Committee (NDPSC)*

The June 2007 NDPSC Meeting agreed that consideration of the scheduling of boron should be deferred, pending information from NZ regarding a potential proposal to set a new exemption cut-off, and the reasons for any such recommendation.

### *December 2007 NZ Medicines Classification Committee (MCC)*

At the December 2007 Meeting, the MCC agreed that boron, including boric acid and borax, should be a prescription medicine except when for internal use in medicines containing 6 mg or less per recommended daily dose; for dermal use other than paediatric use in medicines containing 0.35 per cent or less or when present as an excipient.

### *February and June 2008 National Drugs and Poisons Schedule Committee (NDPSC)*

The February and June 2008 NDPSC Meetings, following reconsideration of the issues (including the reasons for the adoption by New Zealand of a 6 mg cut-off for internal use), agreed to foreshadow the following amendments to the Schedule 4 boron entry (including capture of all paediatric use as Schedule 4) to allow stakeholders a further opportunity to comment, and to help identify any potential unintended consequences:

- Broadening the entry, particularly regarding topical use, by amending from an inclusive to an exclusive form.
- Increasing the internal use cut-off from 3 mg to 6 mg.
- Capturing all dermal paediatric use in Schedule 4 (i.e. remove the current allowance for dermal paediatric use, when not a dusting powder and  $\leq 0.35$  per cent, to be unscheduled).
- Removing the exemption for antifungal preparations for dermal use (i.e. these will be captured in Schedule 4).
- Adding the expression “including boric acid and borax” and changing ‘milligrams’ in part (a) to ‘mg’.

#### ***“Schedule 4 – Foreshadowed amendment***

*BORON – Amend entry to read:*

*BORON, including boric acid and borax, for human therapeutic use **except:***

- a) in preparations for internal use containing 6 mg or less of boron per recommended daily dose;*
- b) in preparations for dermal use containing 0.35 per cent or less of boron, other than preparations other than preparations for paediatric or antifungal use; or*
- c) when present as an excipient.”*

#### ***Australian regulatory information***

Boric acid is an ingredient in 80 products on the [ARTG](#) including eye drops, antifungal treatments, contact lens solution, detergents and vitamins.

Boric acid is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#) as follows:

Ingredient Name	Purpose of the ingredient in the medicine	Specific requirements
890	BORIC ACID	<p>A, H</p> <p>Boron is a mandatory component of Boric acid. The percentage of Boron from Boric acid should be calculated based on the molecular weight of Boric acid</p> <p>The maximum recommended daily dose must provide no more than 6mg of Boron.</p> <p>In preparations for dermal use, which are not for paediatric or antifungal use, the concentration of boron in the medicine must be no more than 3500 mg/kg or 3500 mg/L or 0.35%</p> <p>The indication 'For mineral (may state the mineral) supplementation' is only permitted for use when the medicine is for oral or sublingual use.</p>

Some members of this group (CAS Nos. 1330-43-4, 12267-73-1, 13840-56-7) are classified as hazardous for reproductive and developmental toxicity – Category 1B; H360FD (May damage fertility. May damage the unborn child) in the HCIS (Safe Work Australia).

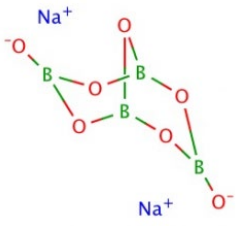
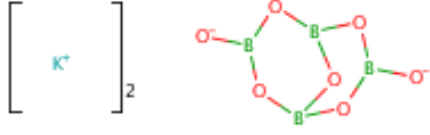
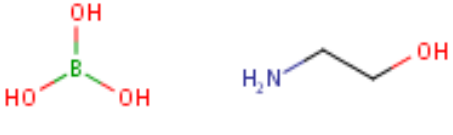


Boric acid (CAS No. 10043-35-3) is classified as a hazardous for reproductive and developmental toxicity – Category 1B; H360FD (May damage fertility. May damage the unborn child) in the HCIS (Safe Work Australia).

### ***International regulations***

Boric acid, disodium salt and boric acid, dipotassium salt are listed on the following:

- European Union (EU) Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products—Annex III— “List of substances which cosmetic products must not contain except subject to the restrictions laid down” with specific conditions on maximum in-use concentrations for talc (5%), oral products (0.1%) and other products (3%). Other conditions include restrictions and label statements to the effect of “Not to be used in products for children under 3 years of age”.
  - The 2013 EU SCCS opinion on “the safety of boron compounds in cosmetic products” recommended further risk management, however this recommendation has not yet been implemented in legislation.
- The chemicals boric acid, disodium salt, MEA-borate and MIPA-borate are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

## Substance summary

 <p><b>1330-43-4</b></p> <p>Boric acid (H<sub>2</sub>B<sub>4</sub>O<sub>7</sub>), disodium salt; Boron sodium oxide, (B<sub>4</sub>Na<sub>2</sub>O<sub>7</sub>) (CAS); Sodium borate (INCI); disodium tetraborate; sodium borate anhydrous; disodium tetraborate, anhydrous</p>	
 <p><b>1332-77-0</b></p> <p>Boric acid (H<sub>2</sub>B<sub>4</sub>O<sub>7</sub>), dipotassium salt; Boron potassium oxide (B<sub>4</sub>K<sub>2</sub>O<sub>7</sub>) (CAS); potassium tetraborate; potassium borate; dipotassium tetraborate</p>	 <p><b>26038-87-9</b></p> <p>Boric acid (H<sub>3</sub>BO<sub>3</sub>), compd. with 2-aminoethanol; monoethanolamine, boric acid salt; Boric acid (H<sub>3</sub>BO<sub>3</sub>), compd. with 2-aminoethanol (1:?) (CAS); MEA-borate (INCI)</p>
 <p><b>26038-90-4</b></p> <p>Boric acid (H<sub>3</sub>BO<sub>3</sub>), compd. with 1-amino-2-propanol (1:?) (CAS); MIPA-borate (INCI); 1-aminopropan-2-ol, compound with orthoboric acid; boric acid, monoisopropanolamine salt; orthoboric acid isopropanolamine salt</p>	 <p><b>68003-13-4</b></p> <p>Boric acid (H<sub>3</sub>BO<sub>3</sub>), compd. with 1-amino-2-propanol (1:1) (CAS); MIPA-borate (INCI); Isopropanolamine borate; (2-hydroxypropyl)ammonium dihydrogen orthoborate</p>

**Figure 2.2.1: Some chemical structures boric acid salts used in cosmetic and domestic products**

The following information was extracted from [the NICNAS IMAP Human Health Tier II assessment report for salts of boric acid](#).

**Table 2.2.1: Acute toxicity end-points for salts of boric acid**

Toxicity	Species	Salts of boric acid	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000 mg/kg bw (for suitable analogues)	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000 mg/kg bw (for suitable analogues)	Schedule 5



Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	>2000 mg/m <sup>3</sup> (for suitable analogues)	Schedule 5
Skin irritation	Rabbit	Suitable analogue chemicals non-irritating.	Schedule 5
Eye irritation	Rabbit	Suitable analogue chemicals produced mild irritation in some studies	Schedule 5
Skin sensitisation	Guinea pig	Suitable analogue chemicals are non-sensitising	Schedule 5

### General statement

The Scientific Committee on Consumer Safety (SCCS) has recently concluded that substances such as borates, tetraborates, and octaborates as well as other boric acid salts/esters (MEA-borate, MIPA-borate, potassium borate, trioctyldecyl borate and zinc borate reported in the CosIng database) produce boric acid following contact with water. Therefore, as these compounds have chemical, biological and toxicological properties similar to boric acid, the general restrictions applicable to boric acid for safe use in cosmetic products should apply to the whole group of borates (SCCS, 2013).

### Acute toxicity

#### Oral

Limited data was provided for the chemicals in this group. The information available for sodium borate, anhydrous (CAS No. 1330-43-4) and analogues boric acid (CAS No. 10043-35-3), borax (CAS No. 1303-96-4) and zinc borates suggest that the chemicals in this group are likely to have low acute toxicity in animal tests following oral exposure. The median lethal dose (LD<sub>50</sub>) in rats for the tested chemicals in the group and the analogue chemicals is >2000 mg/kg bw. The boric acid amine salts are also expected to have low acute oral toxicity (>2000 mg/kg bw).

#### Dermal

No data was provided for the chemicals in this group.

Data available for the analogue chemicals, boric acid (CAS No. 10043-35-3), borax (CAS No. 1303-96-4) and zinc borates indicate that the chemicals in this group are likely to have low acute toxicity in animal tests following dermal exposure. The dermal LD<sub>50</sub> in rats is >2000 mg/kg bw for each of these analogues. It is also noted that the dermal absorption through intact skin is very low (dermal absorption rate of 0.5% was assumed for borates).<sup>52, 53, 54</sup>

<sup>52</sup> National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Tier II human health assessment for boric acid (CAS No. 10043-35-3). Australian Government Department of Health. Available at <http://www.nicnas.gov.au>

<sup>53</sup> National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Tier II human health assessment for borax (CAS No. 1303-96-4). Australian Government Department of Health. Available at <http://www.nicnas.gov.au>

<sup>54</sup> National Industrial Chemicals Notification and Assessment Scheme (NICNASd). Tier II human health assessment for zinc borate (CAS No. 1332-07-6). Australian Government Department of Health. Available at <http://www.nicnas.gov.au>

## **Inhalation**

No data was provided for the chemicals in this group.

Information available on the analogues boric acid (CAS No. 10043-35-3), borax (CAS No. 1303-96-4) and zinc borates indicates that the chemicals in this group are likely to have low acute toxicity in animal tests following inhalational exposure. The highest achievable inhalational dose produced no mortalities in these studies.

## **Observation in humans**

There is a large database of accidental or intentional poisoning in humans following exposure to borates. A review of more than 700 cases of acute boric acid exposures in adults and children found 88.3% of cases were without symptoms. Although the report provided only limited information on dose response, dose ranges of 0.1–55 g and 0.01–89 g of boric acid were reported for symptomatic and asymptomatic cases, respectively. There are case reports of lethal oral exposures in humans involving accidental or intentional ingestion of high doses of boric acid. While oral lethal doses for boric acid have been quoted as 2–3 g for infants, 5–6 g for children, and 15–30 g for adults, the data are largely unsubstantiated. Further difficulty in making an appropriate quantitative judgment about a lethal dose was also noted due to medical intervention in most cases. Following ingestion of a formula accidentally prepared with a 2.5% aqueous solution of boric acid, 5 infants became lethargic, developed vomiting and diarrhoea, and died within 3 days of exposure (estimated dose of 4.5–14 g boric acid). Deaths have also occurred in a 77-year-old man following ingestion of 30 g of boric acid and in a 45-year-old man following ingestion of approximately 280 g of boric acid. In both instances, clinical signs were similar: vomiting, diarrhoea, erythema, cyanotic extremities, acute renal failure, cardiopulmonary hypertension and death from heart failure.

## *Irritation*

### **Skin**

Although the data for the chemicals in this group are limited, the available information on the analogues, boric acid (CAS No. 10043-35-3), borax (CAS No. 1303-96-4), and on zinc borates indicate that the chemicals in this group are not likely to be skin irritants.

### **Eye**

Limited data was provided on the chemicals in this group. In an eye irritation study, potassium pentaborate (CAS No. 11128-29-3) (0.1 g) was placed in the conjunctival sac of the right eye of each of the three New Zealand White (NZW) rabbits and treated eyes were rinsed with water 24 hours after administration of the test substance. The untreated left eye of each rabbit served as a control. As significant eye irritation scores were not observed in any animal throughout the study, the chemical was classified as non-irritant to the eyes. Slight eye irritant effects were reported in animal studies for the analogues: boric acid (CAS No. 10043-35-3); borax (CAS No. 1303-96-4) and on zinc borates. The reported effects were not sufficient to warrant hazard classification for the chemicals in this group.

### **Respiratory**

The limited data indicate that the chemicals in this group are unlikely to be specific respiratory irritants.

### *Sensitization*

Although no information is available on the skin sensitisation potential of chemicals in this group, based on the available information on the analogue chemicals, the chemicals in this group are not likely to be skin sensitisers.

### **Observation in humans**

No evidence of skin or respiratory sensitisation in humans occupationally exposed to borates has been reported.

### *Repeat-dose toxicity*

#### **Oral**

No data was provided for the chemicals in this group.

The available information on boron-containing compounds indicates that the chemicals in this group are not likely to cause serious damage to health from repeated oral exposure.

#### **Dermal**

No data was provided.

#### **Inhalation**

No data was provided.

### *Genotoxicity*

Although the data for the chemicals in this group are limited, the available information on boric acid (CAS No. 10043-35-3) and zinc borates indicates that the chemicals in this group are not likely to have a mutagenic or genotoxic potential.

### *Carcinogenicity*

Limited data are available on the chemicals in this group. Available information on other inorganic borates and on zinc borates indicates that the chemicals in this group are not likely to have a carcinogenic potential. The chemicals in this group are also not considered to have a mutagenic or genotoxic potential.

### *Reproduction and developmental toxicity*

No data was provided regarding reproductive or developmental effects of chemicals in this group in animals and humans, although there are studies on the analogues boric acid and borax. While the appropriate data are not available for chemicals in this group, information on boron-containing compounds (boric acid) in animals is sufficient to support classification for all chemicals in this group.

The testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies, with the rat being the most sensitive species. The reported testicular effects included reduced organ weight and organ:body weight ratio; atrophy and degeneration of the spermatogenic epithelium; impaired spermatogenesis; and reduced fertility. The reported developmental effects included high prenatal mortality; reduced foetal body weight; and malformations and variations of the eyes, central nervous system, cardiovascular system and axial skeleton. The NOAEL for fertility of 100 mg/kg bw/day of boric acid (equivalent to 17.5 mg boron/kg

bw/day) has been determined from two-year and three-year generational studies in rats, based on testicular effects. The critical NOAEL for developmental effects has been determined as 55 mg/kg bw/day of boric acid (equivalent to 9.6 mg boron/kg bw/day) in rats.

As the chemicals in this group dissociate in water and give rise to boric acid, these results are applicable to borate salts.

#### *Public exposure*

Although specific use in cosmetic products in Australia is not known, the chemicals are reported to be used in cosmetic products overseas as buffering agents and viscosity controlling agents.

#### **Pre-Meeting Public Submissions**

Two (2) public submissions were received for salts of boric acid, which opposed the scheduling proposal.

#### *Main points opposed:*

- The five salts of boric acid identified are used at very low concentrations in cosmetics as buffering/viscosity controlling agents (sodium borate), as enzyme stabilisers in domestic detergent products and as corrosion inhibitors in industrial products.
- Borax is present in many preparations for internal use containing 6 mg or less of boron per recommended daily dose as per the Schedule 4 entry. There are also many non-therapeutic products (for example dental adhesive products) which contain borax (as a preservative and viscosity controlling agent) that will be adversely affected by the proposal.
- The current EU concentration cut-offs for cosmetics (talc (5%), oral products (0.1%) and other products (3%)) should be used in the current Schedule 5 entry for boric acid and borax.
- Request a decision deferral pending a thorough investigation of scheduling impact, or an appropriate transition period of 24 to 30 months be applied to allow for any reformulation and/or labelling changes that would be required.

The public submissions will be made available on the [TGA website](#).

#### **Summary of ACCS-ACMS advice to the delegates**

The committee recommended that the Schedule 5 and Index entries of boric acid be amended as follows:

##### **Schedule 5 – Amend Entry**

~~BORIC ACID (excluding its salts) and BORAX~~ **except:**

- a) when included in Schedule 4; or
- b) in preparations, other than insect baits, containing 1 per cent or less **calculated as** ~~of~~ boron; or
- c) in hand cleaning preparations.

##### **Index – Amend Entry**

###### **BORIC ACID**

cross reference: BORAX, **BORON**

The committee also recommended an implementation date of **1 October 2018** to allow time for industry to accommodate the changes.

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

The reasons for the recommendation comprised the following:

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

- The risks of boric acid and its salts is that the data indicates that the hazard is considered:
  - low to moderate effects in humans with normal use;
  - can cause only minor adverse effects to the human being in normal use;
  - requires caution in handling, storage, or use (S5); and
  - may cause death or severe injury if ingested (S6).
- The benefit of boric acid and its salts is that it is used as an excipient to improve products.

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

- Boric acid and its salts are used in a wide range of cosmetics and personal products (antiseptics/astringents/skin lotions/some eyewash solutions/enamels and glazes).
- They are also used in domestic and industrial cleaning products, including dishwashing and laundry liquids.

c) *the toxicity of a substance:*

- There are reproductive and developmental effects in sensitive animals.
  - Testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies.
- Toxicity in humans:
  - No or limited data of oral, dermal and inhalation toxicity and genotoxicity or carcinogenicity.
  - Overall, evidence from studies considered shows toxicity in these areas is low in humans.
  - No appropriate data available for analogues boric acid and borax.
- Salts of boric acid are readily converted to boric acid in aqueous solutions.

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

- Appropriate Warning for:
  - Repeated Use;
  - Ingestion ; and
  - Developmental and Reproductive toxicity.
- Labelling and packaging should restrict use in children and child access to products with higher concentrations.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

### ***Delegates' considerations***

The delegates considered the following in regards to this proposal:

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

### ***Delegates' interim decision***

The delegates' interim decision is to amend the Schedule 5 and index entries for boric acid. The proposed Schedule and index entries are:

#### **Schedule 5 – Amend Entry**

**BORIC ACID except:**

- a) when included in Schedule 4; or
- b) in preparations, other than insect baits, containing 1 per cent or less calculated as boron;  
or
- c) in hand cleaning preparations.

#### **Index – Amend Entry**

##### **BORIC ACID**

cross reference: BORAX, BORON

The proposed implementation date is **1 October 2018**. This is to allow time for industry to accommodate the changes.

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:

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

- The risks of boric acid and its salts is that the data indicates that the hazard is considered:
  - low to moderate effects in humans with normal use;
  - can cause only minor adverse effects to the human being in normal use;
  - requires caution in handling, storage, or use (S5); and

- may cause death or severe injury if ingested (S6).
  - The benefit of boric acids and its salts is that it is used as an excipient to improve products.
- b) the purposes for which a substance is to be used and the extent of use of a substance:
- Boric Acid and its salts are used in a wide range of cosmetics and personal products (antiseptics/astringents/skin lotions/some eyewash solutions/enamels and glazes).
  - They are also used in domestic and industrial cleaning products, including dishwashing and laundry liquids.
- c) the toxicity of a substance:
- There are reproductive and developmental effects in sensitive animals.
    - Testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies.
  - Toxicity in humans:
    - No or limited data of oral, dermal and inhalation toxicity and genotoxicity or carcinogenicity.
    - Overall, evidence from studies considered shows toxicity in these areas is low in humans.
    - No appropriate data available for analogues boric acid and borax.
  - Salts of boric acid are readily converted to boric acid in aqueous solutions.
- d) the dosage, formulation, labelling, packaging and presentation of a substance:
- Appropriate Warning for:
    - Repeated Use;
    - Ingestion; and
    - Developmental and Reproductive toxicity.
  - Labelling and packaging should restrict use in children and child access to products with higher concentrations.
- e) the potential for abuse of a substance:
- Nil.
- f) any other matters that the Secretary considers necessary to protect public health:
- Nil.

## 2.3 Polihexanide

### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the current entry for polihexanide in Schedule 6 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.



### ***Scheduling application***

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

#### **Schedule 6 – Amend Entry**

POLIHEXANIDE **except:**

- a) in preparations containing 50.3 per cent or less of polihexanide; or
- b) when packed and labelled for therapeutic use.

#### **Appendix F, Part 3 – Amend Entry**

POLIHEXANIDE

Warning Statement: 28 (Repeated exposure may cause sensitisation).

Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist).

The applicant's reasons for the request are:

- Polihexanide is a polymer of chlorhexidine (listed in Schedules 5 and 6 of the Poisons Standard).
- Polihexanide has reported cosmetic and domestic uses overseas, as preservative and biocide, in products that are potentially available for use in Australia;
- Polihexanide has moderate acute oral and inhalation toxicity, are highly irritating to the eyes, are moderate skin sensitisers, and present a moderate hazard from repeated inhalation toxicity; and
- Overseas restrictions exist for the use of polihexanide in cosmetic products where the maximum concentration allowed is 0.3%.
- The 2015 Scientific Committee on Consumer Safety (SCCS) Opinion of poly(hexamethylene)biguanide hydrochloride (PHMB) or polihexanide. The Opinion indicated that the chemical is not considered safe as a preservative in all cosmetic products at up to 0.3%.
- The SCCS released the 2017 Opinion of PHMB. The opinion indicated that the safe level of use of polihexanide as a preservative in cosmetic products is 0.1%. As a result of this Opinion, a restriction process in the EU to lower the cut-off is expected in the short- to medium-term. The Cosmetic Ingredient Review (CIR) Expert Panel 2017 safety assessment of polihexanide (currently for public comment) as used in cosmetics. The IMAP Human Health Tier II assessment will be re-published in November 2017 to include these two recent reports.
- While the re-published assessment may recommend further restriction of cosmetic and domestic use concentrations, referral for Scheduling for any further restrictions will need to consider finalisation of any further EU restrictions. This may take some time, and the current absence of a specific restriction on use of polihexanide in cosmetic and domestic products in Australia poses a risk to public health.

### ***Current scheduling status***

Polihexanide is currently listed in Schedule 6 and in Appendices E and F of the Poisons Standard as follows:

#### **Schedule 6**

POLIHEXANIDE **except:**

- a) in preparations containing 5 per cent or less of polihexanide; or

- b) when packed and labelled for therapeutic use.

### **Appendix E, Part 2**

#### **POLIHEXANIDE**

Standard Statement: E1 (If in eyes, wash out immediately with water).

### **Appendix F, Part 3**

#### **POLIHEXANIDE**

Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist).

Chlorhexidine (polihexanide is a polymer of chlorhexidine) is in Schedules 7, 6 and 5 of the Poisons Standard as follows:

#### **Schedule 7**

**CHLORHEXIDINE except:**

- a) when included in Schedule 5 or 6;
- b) in preparations containing 1 per cent or less of chlorhexidine; or
- c) in solid preparations.

#### **Schedule 6**

**CHLORHEXIDINE** in preparations containing 7 per cent or less of chlorhexidine **except:**

- a) when included in Schedule 5;
- b) in preparations containing 1 per cent or less of chlorhexidine; or
- c) when in solid preparations.

#### **Schedule 5**

**CHLORHEXIDINE** in preparations containing 3 per cent or less of chlorhexidine **except:**

- a) in preparations containing 1 per cent or less of chlorhexidine; or
- b) when in solid preparations.

### ***Scheduling history***

#### *May 1977 Poisons Schedule (Standing) Committee (PSC)*

In May 1977, the Poisons Schedule (Standing) Committee (PSC) considered the substance (at that time it was called poly(hexamethylene biguanide) hydrochloride) and decided to list it in Schedule 5 and the then Appendix A (now Appendix E). The reason for these entries was its LD<sub>50</sub> in the rat was 1 g/kg (toxicity end-point details were not provided).

#### *November 1982 Poisons Schedule (Standing) Committee (PSC)*

In November 1982, the PSC considered an application requesting that preparations containing less than 20% of poly(hexamethylene biguanide) be exempted from scheduling. The PSC did not accept the proposal because of concerns over "equivocal" results in developmental studies in rats, low survival rate in sub-acute oral studies in rats, and severe eye irritancy. The PSC, however, agreed to a 5% cut-

off as exempt from scheduling, on the basis that poly(hexamethylene biguanide) was not a skin or eye irritant at that concentration.

#### *November 2000 National Drugs and Poisons Schedule Committee (NDPSC)*

In November 2000, the NDPSC decided to change the nomenclature of the Schedule 5 entry from poly(hexamethylene biguanide) hydrochloride to polihexanide. This decision was to reflect the World Health Organisation's decision to use the International Non-proprietary Name (INN).

#### *November 2014, Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS#10)*

In June 2011, the Australian Pesticides and Veterinary Medicines Authority's (APVMA) released an updated report, 'polihexanide carcinogenicity: analysis of human health risk', based on an OCS evaluation on the carcinogenicity potential of polihexanide. The report indicated that polihexanide has a potential for carcinogenicity in whole-of-life studies in rodents via the oral route, but only at high exposure levels that are unlikely to be encountered in occupational or public settings. Negative results were obtained in an 80-week dermal study in mice. There were no carcinogenic effects on skin. The occurrence of haemangiosarcoma in the liver at the high dose in the dermal study was considered not to be treatment related as it was within historical controls. Polihexanide did not appear to be genotoxic. The OCS evaluation report did not regard carcinogenicity findings in rodents as a barrier to continuing registration of products containing polihexanide.

In September 2014, the Office of Chemical Safety (OCS), based on the APVMA's review on polihexanide, submitted a proposal to delete the current Schedule 5 polihexanide entry and create a new Schedule 6 entry for preparations containing more than 5% of polihexanide. This application was considered at the November 2014 Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS#10). The committee recommended that the current Schedule 5 polihexanide entry be deleted and a new Schedule 6 entry be created for preparations containing more than 5% of polihexanide. The committee also recommended that the new entry specifically exempt from scheduling preparations containing polihexanide when packed and labelled for therapeutic use; and that a First Aid Statement 'E1 - If in eyes wash out immediately with water' be applied. The delegate agreed based on the critical toxicological endpoints driving this categorisation (acute toxicity, severe skin/eye irritancy and sensitisation potential) consistent with SPF criteria for listing in Schedule 6, and given the public health risk sufficiently ameliorated for products under 5 per cent. This was implemented on 1 June 2015.

#### ***Australian regulatory information***

The applicant states that no restrictions in Australia exist for using polihexanide in cosmetic or domestic products.

Polihexanide (as polyhexamethlenebiguanidine) is an ingredient in 8 products on the ARTG including contact lens solution, irrigation fluid for medical/surgical procedures, dental material for root fillings, sanitising wipes and disinfectant spray.

According to the ARTG database, Polyhexamethlenebiguanidine (PHMB) is permitted for use as an excipient in Devices only. It is not currently used in any PI formulations.

There are no recorded adverse events in the [Database of Adverse Event Notifications – media devices](#) for polyhexamethlenebiguanidine.

Polihexanide is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#). However, the similar compound polyaminipropyl biguanide (CAS No. 133029-32-0, Figure 1 below) and chlorhexidine (as the acetate and gluconate) are listed as follows:

Ingredient Name	Purpose of the ingredient in the medicine	Specific requirements
3908	POLYAMINOPROPYL BIGUANIDE	E  Only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye.  The concentration in the medicine must be no more than 0.3%.
1298	CHLORHEXIDINE ACETATE	E  Only for use in topical medicines for dermal application.
1299	CHLORHEXIDINE GLUCONATE	E  Only for use in topical medicines for dermal application.

### ***International regulations***

The chemicals are permitted as preservatives in cosmetic products in the EU and NZ at a maximum permitted concentration of 0.3%.

The use of polihexanide in cosmetics in the European Union (EU) is subject to the EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products. Polihexanide may be used as preservatives in cosmetic products at a maximum permitted concentration of 0.3%. According to the 2017 SCCS opinion a reduction in this concentration was recommended, but this has not yet been finalised, nor implemented in legislation.

Polihexanide are also listed, with similar use restrictions described above, in the NZ Cosmetic Products Group Standard—Schedule 7.

### ***Substance summary***

**Table 2.3.1: Chemical properties for polihexanide**

Property	Polihexanide
CAS numbers	32289-58-0 27083-27-8 28757-47-3 133029-32-0

Chemical structure	$X - ((\text{CH}_2)_3 - \text{NH} - \underset{\text{NH}}{\underset{ }{\text{C}}} - \text{NH} - \underset{\text{NH}}{\underset{ }{\text{C}}} - \text{NH} - (\text{CH}_2)_3)_n - X$ <p>where X = HCl. NH<sub>2</sub> - (CH<sub>2</sub>)<sub>3</sub></p> <p>or X = - (CH<sub>2</sub>)<sub>3</sub> - NH - <math>\underset{\text{NH}}{\underset{ }{\text{C}}} - \text{NH} - \text{CN}</math></p> <p>or X = - (CH<sub>2</sub>)<sub>3</sub> - NH - <math>\underset{\text{NH}}{\underset{ }{\text{C}}} - \text{NH}_2 \cdot \text{HCl}</math></p>
IUPAC, CAS and/or common and/or other names	Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl); polyhexamethylene biguanide (PHMB); 1-(diaminomethylidene)-2-hexylguanidine (IUPAC); Polyaminopropyl Biguanide (INCI)

Polihexanide (polyhexamethylene biguanide hydrochloride or PHMB) is a polymer of chlorhexidine and a preservative ingredient/biocide in cosmetics and domestic products and therapeutic goods including disinfectants and sanitisers.

Polihexanide is used as an active ingredient in various preparations such as wet wipes, wound irrigation solutions, sterile dressings as well as disinfectants (e.g. medical equipment, medical procedures, contact lens cleaners, food preparation surfaces, industrial situations, veterinary products and milk handling equipment). Polihexanide is also used as an antimicrobial for the control of microorganisms, algae and fungi in swimming pools and spas.

Due to its excellent biocidal properties, the usage of polihexanide has increased in personal care products and pharmaceuticals, for instance in the treatment of chronic wounds and burns. This widely used biocide has been reviewed by the US EPA, which noted that the biocide has very low aggregate risk of adverse health effects to the public or environment, except for occupational users.

Polihexanide binds to the negatively charged phosphate head groups of phospholipids on the bacterial cell wall causing increased rigidity by sinking nonpolar segments into hydrophobic domains, and membrane disruption with subsequent cytoplasmic shedding, culminating in cell death. The antibacterial activity of polihexanide depends on its molecular structure. Minimum requirements for biocidal activity are met by having more than 2 biguanide moieties and 5-7 methylene groups as a spacer. Therefore, polihexanide represents an oligomeric substance with a number-average degree of polymerization of 2-5. It is a cationic biocide marketed worldwide, because of its excellent antimicrobial activity, chemical stability, low toxicity and reasonable cost. Polihexanide is highly soluble in water (20%, w/v) and aliphatic alcohols, but poorly soluble in nonpolar liquids. The biguanide moieties are strong bases and monoprotinated at a pH value of 7 (pKa<sub>1</sub>=2-3; pKa<sub>2</sub>=10.5-11.5) resulting in a polycation with a positive charge at each biguanide moiety.<sup>55</sup>

The following information was extracted from the [NICNAS IMAP Human Health Tier II assessment report for polihexanide](#).

### Table 2.3.2: Acute toxicity end-points for polihexanide

<sup>55</sup> Markus Küsters, Sören Beyer, Stephan Kutscher, Harald Schlesinger and Michael Gerhartz. [Rapid, simple and stability-indicating determination of polyhexamethylene biguanide in liquid and gel-like dosage forms by liquid chromatography with diode-array detection \(link is external\)](#). Journal of Pharmaceutical Analysis, Volume 3, Issue 6, December 2013, Pages 408-414.

Toxicity	Species	Polihexanide	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	501-1049 mg/kg bw	Schedule 6
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat, Rabbit	>2000 mg/kg bw	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	0.29-0.48 mg/L/4 hours (290-480 mg/m <sup>3</sup> /4 hours)	Schedule 7
Skin irritation	Rabbit	Slightly irritating	Schedule 5
Eye irritation	Rabbit	Highly irritating	Schedule 6
Skin sensitisation (GPMT, Buehler)	Guinea pig	Moderate	Schedule 6

Polihexanide has moderate acute toxicity based on results from animal tests following oral exposure, with median lethal dose (LD<sub>50</sub>) values ranging from 501-1049 mg/kg bw. Observed sub-lethal effects in these studies included lethargy, ataxia, salivation, laboured breathing, lacrimation, piloerection, and partial drooping of the upper eyelids (ptosis).

Polihexanide has low acute toxicity based on results from animal tests following dermal exposure, with LD<sub>50</sub> values > 2000 mg/kg bw.

Polihexanide has high acute toxicity based on results from animal tests following inhalation exposure, with median lethal concentration (LC<sub>50</sub>) values ranging from 0.29-0.48 mg/L/4 hours. Observed sub-lethal effects in these studies included breathing irregularities, abnormal respiratory noise, partial drooping of the upper eyelids (ptosis), decreased activity and pathological changes in the lungs.

### *Irritation*

Polihexanide, when applied at neat concentrations, is slightly irritating to rabbit skin.

Polihexanide is highly irritating to rabbit eyes.

In a study compliant with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 405, 0.1 mL of neat polihexanide was instilled into the conjunctival sac of one eye of a male New Zealand White (NZW) rabbit. The other eye was used as a control. The treatment-related effects on the cornea, iris, and conjunctivae were evaluated at the following time points: 1, 24, 48, 72 hours; and 7, 14, 21 days. This single treatment resulted in corneal opacity (opalescent), iridial inflammation and severe conjunctival irritation. Additionally, other treatment-related effects observed include vascularisation and pale appearance of the nictating membrane. These changes were not reversible by 21 days. Considering the severity of the effects, no additional animals were used in the study. Although there were no irritation scores provided, polihexanide was considered corrosive to the rabbit eye following this single application.

Similar results to the study above were reported in another neat application of the chemical to NZW rabbits.

### *Sensitisation*

Based on the available information from guideline-compliant studies in animals, polihexanide is considered to be a moderate skin sensitiser.

In an OECD TG 406-compliant guinea pig maximisation study in Alpk:Dunkin Hartley guinea pigs, intradermal induction used 0.06% polihexanide under occlusive conditions for 48 hours. Topical induction was with 20.2% polihexanide solution. The challenge concentrations used were 20.2% and 6% polihexanide under occlusive condition for 24 hours. The ensuing skin reactions were observed and scored 24 or 48 hours following patch removal. In the guinea pigs challenged with 20.2% polihexanide, scattered redness or moderate diffuse redness were observed in 18/20 and 16/20 animals 24 and 48 hours after patch removal, respectively. The average scores for redness were 1.4 at 24 hours and 1.2 at 48 hours. Similar effects were observed in some animals challenged with 6% polihexanide: 5/20 after 24 hours; and 2/20 48 hours after patch removal. The average scores were 0.3 at 24 hours and 0.1 at 48 hours. Under these tests conditions, polihexanide is considered to be a moderate sensitiser. However, the SCCS has noted that, at 20.2%, polihexanide 'should be considered a strong sensitiser according to Regulation (EC) No 1272/2008 (CLP regulation)'.

Results from several other guinea pig maximisation tests and Buehler studies conducted according or comparable to OECD 406 support the observations of the critical study above.

### *Repeat-dose toxicity*

Based on the available information from guideline-compliant studies in animals, polihexanide is not expected to cause serious damage to health following repeated oral or dermal exposure.

Based on the treatment-related effects reported in repeated dose toxicity studies, repeated inhalation exposure to polihexanide is considered to cause serious damage to health.

In a 28-day repeated dose inhalation toxicity study in male and female Wistar-derived [Alpk:APfSD] rats, the no observed adverse effect concentration (NOAEC) for polihexanide was reported to be 0.0239 mg/m<sup>3</sup> (nominal concentration). In this OECD TG 412-compliant study, rats were exposed nose-only to 0.025, 0.25, and 2.5 mg/m<sup>3</sup> polihexanide for 6 hours a day, 5 days a week for 28 days. Measured concentrations were 0.0239 mg/m<sup>3</sup> (particle size range - 0.32-1.30 µm); 0.257 mg/m<sup>3</sup> (particle size range - 0.48-5.06 µm); and 2.47 mg/m<sup>3</sup> (particle size range - 0.67-1.67 µm). The recovery period following treatment was 13 weeks. Changes in bodyweight and food consumption were observed in males exposed to 0.25 or 2.5 mg/m<sup>3</sup> polihexanide. No deaths occurred in any of the treatment groups. Histopathological analysis showed transient changes in the larynx and trachea in animals from the 0.25 and 2.5 mg/m<sup>3</sup> groups. In these groups, increased liver, lung and thymus weights (males only) were reported. Irreversible pneumonitis (severity reduced at the end of the recovery period) and bronchitis were seen in the lungs of animals treated with 2.5 mg/m<sup>3</sup> polihexanide.

The results from a 21-day repeat dose inhalation study conducted in rats (predates establishment of test guidelines) support the observations of the critical study above.

### *Genotoxicity*

Based on the limited available *in vitro* and *in vivo* genotoxicity studies, polihexanide is not considered to be genotoxic.

### *Carcinogenicity*

Based on several studies conducted in accordance with, or comparable to, United States Environmental Protection Agency, and The Organisation for Economic Cooperation and Development test guidelines, polihexanide induced vascular tumours in rats and mice at high doses only. The doses



were above the maximum tolerated dose. As such, the effects may not be relevant under the conditions of human exposure.

#### *Reproduction and developmental toxicity*

Based on the available data from several animal studies, polihexanide is not expected to exhibit reproductive or developmental toxicity.

#### *Observation in humans*

Polihexanide, at concentrations up to 1.5%, was not irritating to the skin in a skin irritation study in human volunteers. In clinical case reports, 0.02% of aqueous polihexanide solution used in the treatment of *Acanthamoeba keratitis* was tolerated by human corneal and conjunctival epithelium.

In an unpublished 2016 report, the Australian Government Department of Health conducted a detailed evaluation of the available skin sensitisation studies and concluded that polihexanide is a possible skin sensitiser in humans in product formulations at 0.5%, with a potential for causing sensitisation at 0.2% in sensitive individuals.

The following case studies have been reported:

- two cases of severe anaphylaxis were reported following contact with a surgical wound treated with hospital disinfectant containing 0.2% polihexanide;
- an 81-year old female patient experienced symptoms of a grade III anaphylaxis with palmar pruritus, flush, swelling of lips, swallowing difficulties, hypotension and loss of consciousness while using a new brand of wet toilet paper (brand name not provided) containing polihexanide as a disinfectant. The patient had no previously known allergies or atopic diseases. Based on the detailed allergy history, the patient had experienced episodes of grade II anaphylaxis during wound care of an existing leg ulcer: once when using a new wound dressing; and twice after wound cleansing with two different disinfectant products. According to the product data sheets (available online), the wound dressing and disinfectants contain the following polihexanide concentrations: 0.3%, 0.02% and 0.1%;
- six out of 1554 patients showed positive skin reactions following patch tests at a concentration of 2.5% polihexanide on individuals with known contact allergen responses to cosmetics and medications;
- no adverse effects were noted following the exposure of 29 patients to a product, a pre-operative antiseptic for cataract surgery containing 0.2% polihexanide; and
- a 2% concentration of polihexanide is capable of causing skin sensitisation which can be elicited from 0.2% from a human repeat insult patch test (HRIPT) of 191 human volunteers.

#### *Public exposure*

There are no cosmetic or domestic uses identified for polihexanide in Australia. However, overseas information indicates such uses are likely in Australia.

#### ***Pre-Meeting Public Submissions***

Three (3) public submissions were received for polihexanide. One (1) submission raised no objections as it outlined that the proposed scheduling amendment would not have any impact on therapeutic goods. One (1) submission was opposed and one (1) submission supported the proposal for cosmetic products, but opposed the proposal for non-cosmetic products.

*Main points in support:*

- Reducing the cut-off concentration for polihexanide from 5% or less to 0.3% or less when used in cosmetics is in line with current EU requirements (SCCS Opinion 2017) for cosmetic use. It is also in line with expert, peer-reviewed assessments which conclude that polyaminopropyl biguanide (PHMB) is not safe at a maximum concentration of 0.3%.

One submission also requested an amendment to the index entry and a longer implementation date:

- There are various synonyms for these 2 substances. For clarity, entries for the following names should be included in the index and cross-referenced to the polihexanide schedule entry: polyhexamethylene biguanide (PHMB), CAS number 28757-47-3 and polyhexamethylene biguanide (PHMB) hydrochloride, CAS number 27083-27-8.
- An adequate transition period would be required to allow for any labelling changes that may be required as these changes could affect products currently in the Australian market with an established history of safe use. There is no evidence that would suggest immediate action is required for the risk management of this substance.

*Main points opposed:*

- The suggested scheduling does not appear to be sufficient to provide a high level of consumer health safety and is inconsistent with current international, expert peer reviewed assessments.
  - The current and sustained presence of polihexanide in the Australian market place has not been properly identified. It is widely used in leave on applications including on sensitive facial skin and newborn and infants.
  - Inappropriate assumptions were made when considering the relevance of the 2014 SCCS report that concluded “On the basis of the data available, the SCCS concludes that Polyaminopropyl Biguanide (PHMB) is not safe for consumers when used as a preservative in all cosmetic products up to the maximum concentration of 0.3%.”
  - Polihexanide is suspected of causing cancer (Carc 2 H351).
  - The 2017 SCCS is of the opinion that the use of polihexanide as a preservative in all cosmetics up to 0.1% is safe. A more appropriate scheduling for leave on cosmetic use is Schedule 6 with a 0.1% concentration limit. For rinse off cosmetic use, a Schedule 5 entry with a 0.1% concentration limit is more appropriate.
- There is no new information since the 2015 scheduling consideration of this substance that would indicate changes to the 5% concentration in non-cosmetic products are necessary.
- According to the 2017 EU SCCS opinion “with respect to potential contribution of exposure from non-cosmetic use to the overall exposure... it is considered that the actual future consumer related exposure to PHMB is considered in practical terms to be very low.”

The public submissions will be made available on the [TGA website](#).

***Summary of ACCS-ACMS advice to the delegates***

The committee recommended that the current Schedule 6, Appendix F and Index entries for polihexanide be amended, as follows:

**Schedule 6 – Amend Entry**

POLIHEXANIDE **except:**

- a) **in cosmetic** preparations containing **5 0.3** per cent or less of polihexanide; or

- b) when packed and labelled for therapeutic use, or
- c) **in other preparations containing 5 per cent or less of polihexanide.**

### **Appendix F, Part 3 – Amend Entry**

#### **POLIHEXANIDE**

Warning Statement: **28 (Repeated exposure may cause sensitisation).**

Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist).

### **Index Entry – Amend Entry**

#### **POLIHEXANIDE**

**cross reference: 1-(diaminomethylidene)-2-hexylguanidine, poly (iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl), polyhexamethylene biguanide (PHMB)**

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- The benefit of polihexanide is that it is an effective preservative.
- The risk of polihexanide is that it is a skin sensitiser at higher concentrations.

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

- Polihexanide is in use in cosmetics and therapeutic goods

c) *the toxicity of a substance:*

- Polihexanide is highly irritating to eyes in rabbit studies and a moderate skin sensitiser in animals; high acute and repeated inhalation toxicity in animals.
- Polihexanide is a known skin sensitiser in humans.

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

- 0.3% of polihexanide aligns with international regulations.

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

- Nil.

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

- Nil.

### ***Delegates' considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS-ACMS 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 amend the Schedule 6, Appendix F and index entries of the Poisons Standard for polihexanide. The proposed entries are:

#### **Schedule 6 – Amend Entry**

POLIHEXANIDE **except:**

- a) in cosmetic preparations containing 0.3 per cent or less of polihexanide; or
- b) when packed and labelled for therapeutic use, or
- c) in other preparations containing 5 per cent or less of polihexanide.

#### **Appendix F, Part 3 – Amend Entry**

POLIHEXANIDE

Warning Statement: 28 (Repeated exposure may cause sensitisation).

Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist).

#### **Index Entry – Amend Entry**

**POLIHEXANIDE**

cross reference: 1-(diaminomethylidene)-2-hexylguanidine, poly (iminocarbonimidoyliminocarbonimidoyl imino-1,6-hexanediyl), polyhexamethylene biguanide (PHMB)

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

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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:

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

- The benefit of polihexanide is that it is an effective preservative.

- The risk of polihexanide is that it is a skin sensitiser at higher concentrations.
- b) the purposes for which a substance is to be used and the extent of use of a substance:
- Polihexanide is in use in cosmetics and therapeutic goods.
- c) the toxicity of a substance:
- Polihexanide is highly irritating to eyes in rabbit studies and a moderate skin sensitiser in animals; high acute and repeated inhalation toxicity in animals.
  - Polihexanide is a known skin sensitiser in humans.
- d) the dosage, formulation, labelling, packaging and presentation of a substance:
- 0.3% of polihexanide aligns with international regulations.
- e) the potential for abuse of a substance:
- Nil.
- f) any other matters that the Secretary considers necessary to protect public health:
- Nil.

## 2.4 Cimicoxib

### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for cimicoxib in Schedule 4 with no exemption or cut-off in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

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

#### **Schedule 4 – New Entry**

#### **CIMICOXIB.**

The applicant's reasons for the request are:

- Cimicoxib, an imidazole derivative, is a non-steroidal anti-inflammatory drug (NSAID) belonging to the coxib group whose mode of action is the selective inhibition of the enzyme cyclo-oxygenase 2 (COX-2).
- Cimicoxib has low acute oral toxicity; the product has low acute oral, dermal, and inhalational toxicity, is a slight skin irritant, a moderate eye irritant, and is a skin sensitiser.
- The product Cimalgex 80 mg Chewable Tablets for Dogs, containing 80 mg cimicoxib, is intended to treat pain in dogs and requires veterinary diagnosis and management (i.e. prescription).
- The Committee has previously considered a number of other NSAID COX-2 inhibitors, such as celecoxib, mavacoxib, rofecoxib and valdecoxib.

### *Current scheduling status and scheduling history*

Cimicoxib is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Related selective COX-2 inhibitors with similar properties are listed in Schedule 4, such as celecoxib, lumiracoxib, mavacoxib and meloxicam.

### **Australian regulatory information**

Cimicoxib is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), or [PubCRIS](#), and is not an excipient or active in any medicines on the [ARTG](#).

Due to the withdrawal of rofecoxib from the market in 2004, the COX-2 inhibitors have been reviewed by the TGA to address safety concerns.

### **International regulations**

#### *European Union (EU)*

Cimicoxib was registered by EMA/CVMP in February 2011 under the trade name Cimalgex. In March 2015, as part of a veterinary pharmacovigilance initiative, it was recommended to add the following warnings to address relatively high number of reports that include renal disorders and renal failure: *"In very rare cases, increases in renal biochemistry parameters were noted. Furthermore, in very rare cases, renal failure has been reported. As for any long term NSAID treatment, renal function should be monitored"*.

- CIMICOXIB was approved for use in certain EU countries in 2011 (Cimalgex, tablets, 8, 30 and 80 mg) as a treatment for pain and inflammation in dogs.
- Marketing Authorisation Numbers EU/2/10/119/001 – EU/2/10/119/012; the Scientific Discussion of the European Public Assessment Report (EPAR) is here: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/veterinary/000162/WC500109399.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/veterinary/000162/WC500109399.pdf).

#### *United Kingdom (UK)*

Cimicoxib is approved for use in the UK for the treatment of pain and inflammation associated with osteoarthritis, and the management of peri-operative pain due to orthopaedic or soft tissue surgery, in dogs.

#### *Other*

Cimicoxib could not be found as being available in the USA or Canada or New Zealand.

### **Substance summary**

**Table 2.4.1: Chemical information for cimicoxib**

Property	CIMICOXIB
CAS name	Benzenesulfonamide, 4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]
CAS numbers	265114-23-6

Chemical structure	
Molecular formula	C <sub>16</sub> H <sub>13</sub> ClFN <sub>3</sub> O <sub>3</sub> S
Molecular weight	381.8 g/mol
IUPAC and/or common and/or other names	IUPAC: 4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1H-imidazol-1-yl]benzenesulfonamide; UR-8880

The following information was extracted from the Human Health Risk Assessment – Technical Report for cimicoxib.

**Table 2.4.2: Acute toxicity end-points for cimicoxib**

Toxicity	Species	Cimicoxib	Product	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Mouse	>2000 (1/6 deaths)	>5000 (rat)	Schedule 5
	Rat	>2000 (no deaths)		
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	No data	>5000	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	No data	-	-
Skin irritation	Rabbit	No data	Slight	Schedule 5
Eye irritation	Rabbit	No data	Moderate	Schedule 5
Skin sensitisation (GPMT)	Guinea pig	No data	Sensitiser	Schedule 6

In response to the above tables the applicant stated:

- Acute toxicity endpoints have been provided against Schedules 5 and 6 of the Scheduling Policy Framework (SPF), but cimicoxib would be more appropriately listed under Schedule 4.
- For the purposes of the APVMA risk assessment, the product toxicity of all three proposed dosage forms of the product was considered under the 80 mg dose as this has the highest concentration of the active constituent of all three products.



- Cimicoxib, an imidazole derivative, is a non-steroidal anti-inflammatory drug (NSAID) whose mode of action is the selective inhibition of the enzyme cyclo-oxygenase 2 (COX-2). The product containing 80 mg cimicoxib is intended to treat pain in dogs and requires veterinary diagnosis and management (i.e. prescription). The Committee has previously considered a number of other NSAID COX-2 inhibitors, such as celecoxib, mavacoxib, rofecoxib and valdecoxib.
- Oral gavage studies in rats indicated that absorption of cimicoxib was essentially complete at a low dose;  $\geq 93\%$ . Cimicoxib was widely distributed to tissues and extensively metabolised undergoing demethylation and subsequent glucuronidation. Excretion was rapid, predominantly in faeces with lesser amounts in urine. Saturation of absorption was observed in rats, rabbits and dogs as well as in a human clinical trial in male adults at oral doses  $>75$  mg cimicoxib. Tissue accumulation did not occur following repeat dosing in dogs.

#### *Acute toxicity*

Based on the available oral and dermal data, cimicoxib has low acute toxicity.

#### *Repeat-dose toxicity*

In short-term repeat-dose oral (gavage) studies in rats and dogs, the primary target organ was the gastrointestinal tract. In rats, deaths were seen that were associated with inflammation/perforation of the small intestine and gastrointestinal adhesions, with secondary septic peritonitis seen at higher dose levels. Clinical signs such as hunched posture, swollen abdomen that was hard to the touch and decreased motor activity were observed. In dogs, emesis, soft faeces/diarrhoea and hidden blood in the faeces were seen, with adverse decreases also seen in RBC count, haemoglobin, haematocrit, total protein and albumin at higher dose levels.

There was no evidence that cimicoxib was neurotoxic or immunotoxic.

#### *Genotoxicity*

Cimicoxib was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays and was negative. It was concluded that cimicoxib is unlikely to pose a carcinogenic risk to humans.

#### *Carcinogenicity*

No studies investigating the chronic toxicity or carcinogenic potential of cimicoxib are available.

#### *Reproduction and developmental toxicity*

In a one-generation rat study, a decrease in the fertility index at the low dose and greater that lacked a dose response and did not obtain statistical significance was considered incidental, compared to controls. A decrease was also seen in the mean number of corpora lutea. No historical control data were provided, although obtained data on the background incidence of corpora lutea in rats indicated that it was likely to be incidental to treatment. A treatment-related and adverse decrease was seen in uterus weight, the number of implantations and live fetuses, and an increase in the percentage of resorptions and pre- and post-implantation loss in the absence of parental toxicity.

In a study of developmental toxicity in rats, a slight increase was seen in the foetal and litter incidence of haemorrhagic liver, pale liver, malpositioned kidneys and misaligned sternbrae at the top dose level, compared to controls. No historical control data were provided, although data on the background incidence of misaligned sternbrae in rat fetuses indicated it was likely incidental to treatment. No historical control data were identified for haemorrhagic liver, pale liver and malpositioned kidneys in rat fetuses. However, noting that these minor visceral abnormalities were observed in control fetuses and the slight increase seen at the top dose level (that produced deaths

and adhesion and perforation in the small intestine of dams) did not obtain statistical significance, it is considered they were likely incidental to treatment.

In a study of developmental toxicity in rabbits, an increased incidence of total external and internal (visceral) macroscopic abnormalities was seen in foetuses at the low dose and greater in the absence of maternal toxicity at the low and mid dose, compared to controls. At the mid and greater doses, a decrease was seen in uterus weight, increase in percentage post-implantation loss and resorptions and decrease in the number of live foetuses. At the top dose compared to controls, an increase was seen in the foetal incidence of cleft palate, gastroschisis, enlarged fontanelle, absence of 1 or 2 sternebrae and fused sternebrae along with an increase in the litter incidence of enlarged fontanelle and fused sternebrae were seen in the presence of maternal toxicity (mortality, decreased bodyweight gain and gastric perforation and gastrointestinal fibrous adherences in dams). It was concluded that cimicoxib is a reproductive toxicant in rats and teratogenic in rabbits but not rats.

#### *Observation in humans*

In a human clinical trial study in males (aged 18-45 years), cimicoxib was safe and well tolerated following a single oral does up to 600 mg, the highest dose administered.

#### ***Pre-Meeting Public Submissions***

No public submissions were received for cimicoxib.

#### ***Summary of ACCS-ACMS advice to the delegates***

The committee recommended that Cimicoxib be entered into Schedule 4 as follows:

##### **Schedule 4 – New Entry**

##### **CIMICOXIB.**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- The benefit of cimicoxib is that it is an additional anti-inflammatory pain relief option for veterinary use.
- The risk posed by cimicoxib is that if it is used inappropriately (e.g. without health professional prescribing) it may cause serious adverse effects and death.
- Risk and benefit profile consistent with other COX-2 inhibitors and NSAIDs.

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

- It will be used for pain relief in dogs, the management of which requires veterinary intervention.
- Currently not in use in Australia.

c) *the toxicity of a substance:*

- Cimicoxib shows low acute oral, dermal, and inhalational toxicity. Cimicoxib is a slight skin irritant, a moderate eye irritant and is a skin sensitiser.
- Repeat dose toxicity causes ulcerative gastritis in doses close to recommended dose. Reproductive toxicity and teratogenicity (at all doses tested in rabbits) has also been demonstrated.
- Toxicity is consistent with a Schedule 5 or 6 listing, however a Schedule 4 listing is considered appropriate due to the need for veterinary intervention for management of pain in dogs.

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

- Nil.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

### ***Delegates' considerations***

The delegates considered the following in regards to this proposal:

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

### ***Delegates' interim decision***

The delegate's interim decision is create a new Schedule 4 entry for cimicoxib. The proposed Schedule entry is:

#### **Schedule 4 – New Entry**

CIMIXOXIB.

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- The benefit of cimicoxib is that it is an additional anti-inflammatory pain relief option for veterinary use.
- The risk posed by cimicoxib is that if it is used inappropriately (e.g. without health professional prescribing) it may cause serious adverse effects and death.
- Risk and benefit profile consistent with other COX-2 inhibitors and NSAIDs.

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

- It will be used for pain relief in dogs, the management of which requires veterinary intervention.
- Currently not in use in Australia.

c) the toxicity of a substance:

- Cimicoxib shows low acute oral, dermal, and inhalational toxicity. Cimicoxib is a slight skin irritant, a moderate eye irritant and is a skin sensitiser.
- Repeat dose toxicity causes ulcerative gastritis in doses close to recommended dose. Reproductive toxicity and teratogenicity (at all doses tested in rabbits) has also been demonstrated.
- Toxicity is consistent with a Schedule 5 or 6 listing, however a Schedule 4 listing is considered appropriate due to the need for veterinary intervention for management of pain in dogs.

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

- Nil.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

### 3. Advisory Committee on Chemicals Scheduling (ACCS #21)

#### Summary of delegate's interim decisions

Substance	Interim Decision
Fluralaner	<b>Schedule 4 – New Entry</b> FLURALANER <b>except</b> when included in Schedule 5. <b>Index – Amend Entry</b> <b>FLURALANER</b> cross-reference: CARBAMOYL BENZAMIDE PHENYL ISOXAZOLINE Schedule 4 Schedule 5 <i>The proposed implementation date is <b>1 June 2018</b>.</i>
Metofluthrin	<b>Schedule 5 – Amend Entry</b> METOFLUTHRIN: a) in impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per

	<p>disk; or</p> <p>b) when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin.</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Alpha-cypermethrin	<p><b>Schedule 6 – Amend Entry</b></p> <p>ALPHA-CYPERMETHRIN:</p> <p>a) in aqueous preparations containing 30 per cent or less of alpha-cypermethrin; or</p> <p>b) in other preparations containing 10 per cent or less of alpha-cypermethrin,</p> <p><b>except</b> when included in Schedule 5.</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Silver oxide	<p><b>Appendix B – New Entry</b></p> <p>SILVER OXIDE</p> <p>Reasons for Entry: b (Use pattern restricts hazard) Areas of Use: 7.14 (Spa/pool sanitiser)</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives	<p><b>Schedule 6 – Amend Entry</b></p> <p>1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-ACYL DERIVATIVES</p> <p>a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N-acyl derivatives when labelled with a warning statement to the following effect:</p> <p style="text-align: center;">IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or</p> <p>b) in household cleaning preparations, other than those intended to be sprayed, containing 12 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N-acyl derivatives when labelled with a warning statement to the following effect:</p> <p style="text-align: center;">IF IN EYES WASH OUT IMMEDIATELY WITH WATER.</p> <p><b>Index – Amend Entry</b></p> <p><b>1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N- ACYL DERIVATIVES</b> cross-reference: COCOYL METHYL GLUCAMIDE, LAUROYL METHYL GLUCAMIDE, MYRISTOYL METHYL GLUCAMIDE</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Phenyl methyl pyrazolone	<p><b>Schedule 6 – New Entry</b></p> <p>PHENYL METHYL PYRAZOLONE <b>except</b> when used in hair dye and</p>

	<p>eyebrow/eyelash preparations at a concentration of 0.25 per cent or less after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p>KEEP OUT OF REACH OF CHILDREN, and</p> <p>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.</p> <p>written in letters not less than 1.5 mm in height.</p> <p><b>Appendix E, Part 2 – New Entry</b></p> <p>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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p> <p><b>Appendix F, Part 3 – New Entry</b></p> <p>Warning Statement: 28 ((Over) (repeated) exposure may cause sensitisation).</p> <p>Safety Direction: 4 (Avoid contact with skin).</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Dinotefuran	<p><b>Schedule 5 – Amend Entry</b></p> <p>DINOTEFURAN <b>except</b> in preparations containing 1 per cent or less of dinotefuran.</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>
Afidopyropen	<p><b>Appendix B – New Entry</b></p> <p>AFIDOPYROPEN.</p> <p>Reasons for Entry: b (Use pattern restricts hazard) Areas of Use: 1.2 (Insecticide)</p> <p><i>The proposed implementation date is 1 June 2018.</i></p>

### 3.1 Fluralaner

#### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the current entry for fluralaner in Schedule 5 to broaden the use to include products for external use on cats and dogs in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### *Scheduling application*

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

## Schedule 5 – Amend Entry

FLURALANER for the treatment and prevention of flea infestations and control of ticks in dogs in oral ~~as a topical or oral veterinary parasiticide for dogs or cats in~~ divided preparations each containing 1400 mg or less of fluralaner per dosage unit.

The applicant's reasons for the request are:

- Fluralaner presents a low hazard from repeated use and is unlikely to produce irreversible toxicity or other significant toxicity.
- The risk of accidental ingestion by a child is limited by child resistant packaging and appropriate warnings to keep the product out of reach of children.
- Two members of the isoxazoline class, afoxolaner and fluralaner, are in Schedule 5; sarolaner is in Schedule 6, except when included in Schedule 5 (for the treatment, prevention and control of fleas and ticks in dogs in oral divided preparation each containing 120 mg or less of sarolaner per dosage unit).

### Current scheduling status

Fluralaner is currently listed in Schedules 5 as follows:

#### Schedule 5

FLURALANER for the treatment and prevention of flea infestations and control of ticks in dogs in oral divided preparations each containing 1400 mg or less of fluralaner per dosage unit.

Related ectoparasiticides afoxolaner and sarolaner are in the Poisons Standard as follows:

#### Schedule 5

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

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

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

#### Schedule 6

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

### Scheduling history

In August 2014, the Office of Chemical Safety (OCS) [based on an application made to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register a new active ingredient and the approval of five different tablets containing various concentrations of Fluralaner] submitted a proposal to create a new Schedule 5 listing for oral divided preparations, each containing 1400 mg or less of fluralaner per dosage unit, for the treatment and prevention of flea infestations and control of ticks in dogs. The delegate noted the following in the [October 2014 final decision for Fluralaner](#):

*“Fluralaner belongs to a novel class of ectoparasiticides (isoxazoline-substituted benzamide derivatives), two other members of which have been listed in Schedule 5 (isoxaflutole and afoxolaner). The toxicology package indicates that fluralaner also has a sufficiently low acute toxicity profile to be consistent with SPF criteria for listing in Schedule 5. The acute poisoning risk to humans (in particular*



*children) is low, partly associated with the proposed packaging of only four tablets in blister packaging. The delegate considered whether Schedule 4 listing could be more appropriate, providing for oversight of treatment by a veterinarian, noting that this is a condition imposed for registration in the USA, but in the end decided against this, on the basis that the treatment instructions are sufficiently clear that pet owners should be able to manage the required dosage regimen.”*

In October 2014, the delegate made a decision to create a new Schedule 5 entry for Fluralaner in the Poisons Standard for the treatment and prevention of flea infestations and control of ticks in dogs in oral divided preparations each containing 1400 mg or less of fluralaner per dosage unit. This was implemented on 1 February 2015.

Two other ectoparasiticides afoxolaner and sarolaner, also used for treatment of flea infestations and control of ticks in dogs, were all recently considered for scheduling:

- In April 2014, the delegate made a decision to list afoxolaner in Schedule 5 for oral divided preparations of 1400 mg doses; this decision was based on its low acute toxicity profile. The delegate noted that more significant toxicity would be expected with repeated dosage, due to accumulation of active drug. The acute poisoning risk to humans (in particular children) was deemed low, in part due to the proposed packaging of only six tablets in a blister pack.
- In March 2016, the delegate made a decision to create a new Schedule 6 entry for sarolaner with a cut-off for oral divided preparations containing 120 mg or less per dose in Schedule 5. The reasons for the Schedule 6 entry were due to the toxicology profile being more consistent with Schedule 6. However, as the acute poisoning risk is low, the delegate agreed to a Schedule 5 entry, and this is consistent with other ectoparasiticides.

### ***Australian regulatory information***

Fluralaner is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#). Fluralaner is neither an excipient nor active in any medicines on the [ARTG](#).

Fluralaner is the active constituent of approved veterinary medicines (oral chews for dogs for the treatment and prevention of flea infestations and control of ticks). Five (5) products are currently registered by the APVMA.

### ***International regulations***

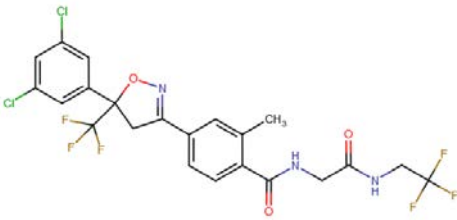
Fluralaner (as a chewable tablet) was approved for use in the EU and US in 2014, with the spot-on being approved in both jurisdictions in 2016. It is available as a spot-on by prescription for use on dogs and cats for the treatment of fleas and ticks for up to 12 weeks. It is available as a 280 mg/mL solution; the largest pipette contains 1400 mg.

- In December 2013, the Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency recommended the granting of a marketing authorisation for the veterinary medicinal product XXXX chewable tablets for dogs (112.5 mg, 250 mg, 500 mg, 1000 mg, 1400 mg) containing fluralaner.
- In May 2014, the US Food and Drug Administration (US FDA) approved fluralaner with a condition that the products containing the substance may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to advise dog owners regarding use in breeding dogs, to monitor for and respond to adverse reactions, and to define the appropriate treatment interval (8 vs. 12 weeks) based on the species of ticks the dog is likely to encounter. Topical solutions are at 280 mg/mL of fluralaner, whereby application is at 25 mg/kg bw, for indications of adult flea or tick treatment.

Fluralaner is also available as a spot-on and chewable tablet in other countries including Canada and New Zealand.

### Substance summary

**Table 3.1.1: Chemical information for fluralaner**

Property	Fluralaner
CAS number	864732-61-3
Chemical structure	
Molecular formula	C <sub>22</sub> H <sub>17</sub> C <sub>12</sub> F <sub>6</sub> N <sub>3</sub> O <sub>3</sub>
Molecular weight	556.3 g/mol
IUPAC and/or common and/or other names	4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4H-1,2-oxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]benzamide (IUPAC)

Fluralaner is a isoxazoline that has shown potent acaricidal and insecticidal activity through a dual mechanism of binding to neuronal  $\gamma$ -aminobutyric acid (GABA)- and glutamate-gated chloride channels in susceptible invertebrates.

Fluralaner has high selectivity for arthropods and a very favourable safety profile in vertebrates including dogs.<sup>56</sup> It is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA receptor and glutamate-receptor). In molecular on-target studies on insect GABA receptors of flea and fly, fluralaner is not affected by dieldrin resistance.

**Table 3.1.2: Acute toxicity end-points for fluralaner**

Toxicity	Species	Fluralaner	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	> 2000	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000	Schedule 5

<sup>56</sup> [Fluralaner, a novel isoxazoline, prevents flea \(\*Ctenocephalides felis\*\) reproduction \*in vitro\* and in a simulated home environment \(link is external\)](#). Heike Williams, David R Young, Tariq Qureshi, Hartmut Zoller, and Anja R Heckerroth. Parasit Vectors. 2014; 7: 275. Published online Jun 19, 2014. doi:10.1186/1756-3305-7-275.

Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	No data	-	N/A
Skin irritation	Rabbit	Nil	N/A
Eye irritation	Rabbit	Nil	N/A
Skin sensitisation (Maximisation test)	Guinea pig	Negative	N/A

### *Acute toxicity*

The delegate previously considered the acute toxicity of fluralaner and no new information is available.

### *Repeat-dose toxicity*

The delegate previously considered short-term studies by both the oral and dermal route of exposure in rats, the main signs associated with treatment included minor variations in haematological and blood chemistry parameters, and organ weight changes. Of the organ weight changes, the liver was the most affected with increases in liver weights associated with fatty changes (diffuse and mid-zonal). The route of exposure did not markedly change the effects seen in treated animals, with similar haematological, blood chemistry and organ weight changes in both orally and dermally treated rats. Additional treatment-related findings in the oral toxicity study included thymic atrophy, zymogen depletion in the pancreas and diffuse vacuolation/hypertrophy in the adrenal cortices at high doses. In more recent dermal and oral 28 day and 90 day repeat-dose studies in rats the main signs associated with treatment at high doses again included similar effects on the liver, thymus and adrenals, as well as the lungs (inflammatory lesions).

### *Mutagenicity*

The delegate previously considered the mutagenicity of fluralaner and no new information is available. There was no evidence of a mutagenic and/or genotoxic potential *in vitro*, with and without metabolic activation, or *in vivo*.

### *Genotoxicity*

The delegate previously considered the genotoxicity of fluralaner and no new information is available. Fluralaner was not genotoxic in a standard suite of *in vitro* and *in vivo* genotoxicity studies.

### *Carcinogenicity*

No carcinogenicity studies have been submitted in support of fluralaner. The use pattern of the spot-on as a quarterly or half-yearly treatment in a non-food-producing use situation, and noting the relatively minor effects seen in short-term studies and the lack of any positive genotoxicity potential, the long-term toxicity potential associated with the proposed use of the active constituent as a veterinary medicine for companion animals (cats and dogs) is likely to be low.

### *Reproduction and developmental toxicity*

The delegate previously considered developmental toxicity studies in the rat. Minor effects were seen in treated fetuses, such as a slight decrease in foetal bodyweights, increases in dilated renal pelvis and ureter, and supernumerary ribs. The effects, however, were at dose levels where maternal effects (decreased food consumption and bodyweight gain) were observed, suggesting foetal effects were

secondary to maternal toxicity. In a more recent pivotal one-generation oral study in rats, fluralaner had effects on the thymus (reduction in weight and lymphoid atrophy) of foetuses and caused a slight reduction in implantation rates and post-implantation losses at high doses resulting in a slight reduction of living pups at the first litter check. In rabbits, high oral doses of fluralaner had effects on the foetal skeleton (cervical vertebra fusion, and reduced fore- and hind-limb ossification) as well as increases in dilated renal pelvis and ureter.

#### *Observation in humans*

No information provided.

#### *Public exposure*

The APVMA will conduct a risk assessment for users of the product as well for bystanders who may have incidental contact with the treated animal or product. The product hazard and exposure risks will be mitigated through label First Aid Instructions and Safety Directions. Any acute exposure is expected to be limited through the product being applied in small dose volumes (up to 5 mL). Also, the product will be supplied packs containing no more than two pipettes each enclosed in a child-resistant sachet (laminated polyester aluminium foil sachet). Acute exposure in the home is expected to be further limited by administration being no less than every three months for an individual animal.

#### *Pre-meeting public submissions*

No submissions were received.

#### *Summary of ACCS advice to the delegate*

The committee recommended that the Schedule 5 entry for fluralaner remains appropriate. However, a new Schedule 4 entry should be created for fluralaner, along with an amendment to the index entry as follows:

##### **Schedule 4 – New Entry**

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

##### **Index – Amend Entry**

**FLURALANER**

**cross-reference: CARBAMOYL BENZAMIDE PHENYL ISOXAZOLINE**

**Schedule 4**

**Schedule 5**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- Risks: there is uncertainty around the human exposure risk and indirect exposure from contact with treated animals.

- Benefit: fluralaner shows longer-lasting flea and paralysis tick prevention compared to other available products.

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

- The proposed use in topical spot-on preparations is likely to result in it being perceived by the public to be as safe as other scheduled spot-on flea treatments that are in wide use and have a relatively longer market history in Australia.

c) the toxicity of a substance:

- The evaluation of the new data since the previous scheduling decision is incomplete.
- There is no human exposure estimation or risk assessment provided.

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

- The topical formulation compared to the oral formulation may contribute to unacceptable public exposure and higher MOEs, including from scheduled excipients, and so requires scheduling at a higher level than the current oral formulation.
- The proposed formulation may present increased risks of accidental exposure compared to the oral formulation.

e) the potential for abuse of a substance:

- Nil.

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

- Refer to the [previous scheduling decision](#).
- There has been reported misuse of existing pet spot-on flea preparations for the treatment of head lice in children in Australia.
- The recommendation for Schedule 4 is consistent with decisions from international jurisdictions.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- 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 Schedule 4 entry for fluralaner, along with a cross-reference in the index to carbamoyl benzamide phenyl isoxazoline. The proposed Schedule entry is:

#### **Schedule 4 – New Entry**

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

#### **Index – Amend Entry**

## FLURALANER

cross-reference: CARBAMOYL BENZAMIDE PHENYL ISOXAZOLINE

Schedule 4

Schedule 5

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

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

- Risks: there is uncertainty around the human exposure risk and indirect exposure from contact with treated animals.
- Benefit: fluralaner shows longer-lasting flea and paralysis tick prevention compared to other available products.

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

- The proposed use in topical spot-on preparations is likely to result in it being perceived by the public to be as safe as other scheduled spot-on flea treatments that are in wide use and have a relatively longer market history in Australia.

c) the toxicity of a substance:

- The evaluation of the new data since the previous scheduling decision is incomplete.
- There is no human exposure estimation or risk assessment provided.

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

- The topical formulation compared to the oral formulation may contribute to unacceptable public exposure and higher MOEs, including from scheduled excipients, and so requires scheduling at a higher level than the current oral formulation.
- The proposed formulation may present increased risks of accidental exposure compared to the oral formulation.

e) the potential for abuse of a substance:

- Nil.

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

- Refer to the [previous scheduling decision](#).
- There has been reported misuse of existing pet spot-on flea preparations for the treatment of head lice in children in Australia.
- The recommendation for Schedule 4 is consistent with decisions from international jurisdictions.

## 3.2 Metofluthrin

### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 5, subclause b entry for metofluthrin to remove '*for use as a mosquito repellent*' in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

### *Scheduling application*

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

#### **Schedule 5 – Amend Entry**

METOFLUTHRIN:

- a) in impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per disk; or
- b) when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin ~~for use as a mosquito repellent~~.

The applicant's reasons for the request are:

- The overall toxicity, oral toxicity and risk of inhalation toxicity of metofluthrin are low.
- The formulation of the proposed product mitigates risk as it is in a polyethylene slow release matrix.
- The main risk of children's inhalation toxicity was found to be at acceptable levels independently of the proposed product use.

### *Current scheduling status*

Metofluthrin is in Schedule 5 and 6 of the Poisons Standard as follows:

#### **Schedule 6**

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

#### **Schedule 5**

METOFLUTHRIN:

- a) in impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per disk; or
- b) when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin for use as a mosquito repellent.

### *Scheduling history*

In February 2011, the Advisory Committee on Chemicals Scheduling (ACCS) considered a proposal to include metofluthrin in Schedule 6. This was based on its toxicity profile of moderate acute inhalation toxicity and neurotoxicity (with clinical signs of neurotoxicity seen at 100 mg/kg bw in a rat acute neurotoxicity study, and at 30 mg/kg bw/d in a 12-month oral study in dogs and in dams in an oral rat developmental study). This was recommended by the ACCS and agreed to by the delegate. The ACCS recommended a new Schedule 6 entry be created for metofluthrin. The delegate decided that the



recommendations of the ACCS were clear and appropriately supported and included metofluthrin in Schedule 6. The delegate decided that a 6 month implementation period was appropriate.

In July 2014, the delegate referred a proposal to the ACCS to amend the current Schedule 6 to exclude mosquito repellent preparations containing 312 g/kg or less of metofluthrin from scheduling. The applicant indicated that the toxicity of the product (the substance impregnated onto non-woven polyester fabric, which is incorporated in a device that is designed to release the substance in the atmosphere) is the same as the toxicity of the substance. The committee recommended that, based on the toxicity profile and use pattern/exposure to the product, the current Schedule 6 metofluthrin entry be amended to exempt impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per disk to Schedule 5. They recommended that the schedule 5 entry should specifically include the preparation and the refill. The delegate accepted the advice provided by the ACCS and decided to include a new entry for metofluthrin in Schedule 5 and to amend the current Schedule 6 entry. The implementation date for this decision was 1 February 2015.

In March 2015, the ACCS considered a proposal to amend the Schedule 5 entry of metofluthrin to allow it to be used in an impregnated woven polyethylene sheet containing 250 mg or less of metofluthrin. While metofluthrin is a moderately toxic pyrethroid insecticide, the packaging and presentation of the product, i.e. the polyethylene slow release matrix and the overall low toxicity, and risk of inhalation toxicity was considered to be low due to the formulation of the product. This was considered to mitigate the overall exposure risk and warranted inclusion in Schedule 5. The committee recommended that the current Schedule 5 listing for metofluthrin be amended to include preparations impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin. The delegate agreed and made a [final decision for metofluthrin on 22 July 2017](#).

### ***Australian regulatory information***

Metofluthrin is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

There are no reported adverse events or safety issues in the [Database of Adverse Events Notifications \(DAEN\)](#) from 1971 to 2017 for methfluthrin.

Metofluthrin is not listed in the [Australian Inventory of Chemical Substances](#) (AICS).

One active constituent and two registered products were found on the [PubCRIS](#) database. Both registered products are for household use for mosquito control/repellent.

### ***International regulations***

#### *European Union (EU)*

Metofluthrin is included in Annex I of the Directive 98/8/EC. Biocidal products containing active substances that have been included in Annex I or IA of the Biocides Directive are subject to product authorisation or registration, respectively, as per the requirements of the Biocides Directive.

As of 23 July 2017, metofluthrin is not on the registered substances database

#### *United States of America (USA)*

In New York State, two products containing metofluthrin have been registered with the following condition:

*'The registrant is required to provide us with a summary of any adverse effects that have been associated with these products, including any FIFRA 6(a)(2) reports, on a quarterly basis.'*

The US Environment Protection Authority (EPA) issued the [metofluthrin Pesticide Fact Sheet](#) in September 2006 (EPA Chemical Code 109709).

### New Zealand (NZ)

In April 2015, the New Zealand EPA approved the importation of metofluthrin as strips impregnated with 312 g/kg of metofluthrin. Each strip contains 13 mg of metofluthrin as part of a refill cartridge for a portable vaporiser to be used by the general public during outdoor activities.

### Canada

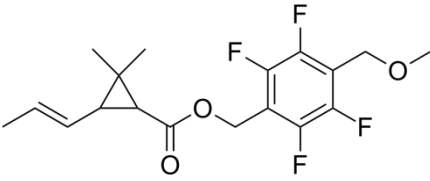
In October 2011, another product was registered for use as a personal insect repellent. Within the first year of its registration, the Pest Management Regulatory Agency (PMRA) received six human incident reports associated with this product. A wide range of symptoms such as dizziness, swelling, nausea, lethargy, muscular weakness, pruritus, irregular heart rate, or loss of consciousness was noted. The effects reported were considered to be either possibly or probably related to pesticide exposure. The product currently holds a registration that is conditional upon the submission of additional data on product exposure. The PMRA indicated that:

*'Although only a few incidents were reported, this is a new product and the PMRA will continue to monitor incidents reported in the following year'.*

In 2016, the Canadian Pest Management Regulatory Agency approved metofluthrin in similar to the NZ clip-on devices. [The Canadian evaluation report](#) is publicly available.

### Substance summary

**Table 3.2.1: Chemical information for metofluthrin**

Property	Metofluthrin
CAS name	[2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl 2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate
CAS number	240494-70-6
Chemical structure	
Molecular formula	C <sub>18</sub> H <sub>20</sub> F <sub>4</sub> O <sub>3</sub>
Molecular weight	360.3 g/mol
IUPAC and/or common and/or other names	(2,3,5,6-tetrafluoro-4-methoxymethylphenyl)methyl-2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate; [2,3,5,6-tetrafluoro-4-(methoxymethyl)phenyl]methyl 2,2-dimethyl-3-[(E)-prop-1-enyl]cyclopropane-1-carboxylate (IUPAC); (2,3,5,6-tetrafluoro-4-methoxymethylphenyl)methyl-2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate;

	Metofluthrin
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Metofluthrin is a synthetic pyrethroid ester insecticide. This class of chemicals act on the nervous system of insects, disturbing the function of neurons by interacting with sodium channels.

Other pyrethroid insecticides include transfluthrin, permethrin, deltamethrin, esfenvalerate and alpha-cypermethrin. While some of these share structural similarity with metofluthrin, this does not appear to be sufficient to class metofluthrin as a derivative (for the purpose of scheduling) of any of these compounds.

The following information was extracted from APVMA assessment report - Human Health Risk Assessment Technical Report – metofluthrin.

**Table 3.2.2: Acute toxicity end-points for metofluthrin**

Toxicity	Species	Metofluthrin	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	>1080 and ≤ 1960	Schedule 6
Skin irritation	Rabbit	Slight irritant	Schedule 5
Eye irritation	Rabbit	Non-irritant	Schedule 5
Skin sensitisation (Guinea Pig Maximisation Test)	Guinea pig	Non-sensitiser	Schedule 5

Hazard profiles of metofluthrin and of the product containing 250 mg or less of metofluthrin impregnated into a polyethylene slow release matrix have previously been considered at the [March 2015 ACCS scheduling meeting](#).

After conducting an online search for metofluthrin toxicology data, the APVMA concludes that these hazard profiles remain appropriate.

It is noteworthy that although metofluthrin was a slight skin irritant, the proposed product containing 250 mg or less of metofluthrin impregnated into a polyethylene slow release matrix was a non-irritant to rabbit skin.

The previous assessment of the product, supporting the “metofluthrin July 2015 scheduling decision”, considered the main concern to be exposure by inhalation, especially in toddlers and young children. The APVMA estimated the theoretically maximum attainable metofluthrin concentration in air, noting that this approach is very conservative, and that the actual metofluthrin concentration in air is always less than the theoretically maximum attainable concentration. Using the theoretically maximum attainable metofluthrin concentration in air, the APVMA estimated the inhalation exposure for 1-2 year old children, and concluded that exposure to the product was unlikely to pose an unacceptable health risk (margins of exposure at 20°C and 35°C were 1350 and 204, respectively).

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACCS advice to the delegate***

The committee recommended that the Schedule 5 entry for metofluthrin be amended as follows:

#### **Schedule 5 – Amend Entry**

METOFLUTHRIN:

- a) in impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per disk; or
- b) when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin ~~for use as a mosquito repellent.~~

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- Risks: the proposed amendment presents no increased risk compared with current scheduling.
- Benefits: the chemical is a highly effective pyrethroid insecticide, which is beneficial for Queensland, particularly Far North Queensland, due to the high incidence of mosquito borne diseases during wet season.

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

- Broad applications to other insect pests.

c) *the toxicity of a substance:*

- Metofluthrin has overall low toxicity, and the risk of inhalation of the product is low due to its formulation.

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

- Polyethylene slow release matrix mitigates risk of toxicity of the product.

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

- Nil.

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

- Nil.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal

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

### ***Delegate's interim decision***

The delegate's interim decision is to amend the Schedule 5 entry for metofluthrin by removing the phrase "*for use as a mosquito repellent*" from subclause (b). The proposed Schedule entry is:

#### **Schedule 5 – Amend Entry**

##### **METOFLUTHRIN:**

- a) in impregnated fabric mosquito repellent preparations for use in a vaporiser containing 15 mg or less of metofluthrin per disk; or
- b) when impregnated into a polyethylene slow release matrix containing 250 mg or less of metofluthrin.

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

The reasons for the interim decision are the following:

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

- Risks: the proposed amendment presents no increased risk compared with current scheduling.
- Benefits: the chemical is a highly effective pyrethroid insecticide, which is beneficial for Queensland, particularly Far North Queensland, due to the high incidence of mosquito borne diseases during wet season.

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

- Broad applications to other insect pests.

c) *the toxicity of a substance:*

- Metofluthrin has overall low toxicity, and the risk of inhalation of the product is low due to its formulation.

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

- Polyethylene slow release matrix mitigates risk of toxicity of the product.

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

- Nil.

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

- Nil.

### 3.3 Alpha-cypermethrin

#### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the current entry for alpha-cypermethrin in Schedule 6 to increase the cut-off in aqueous preparations from 25 per cent or less to 30 per cent or less in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### *Scheduling application*

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

##### **Schedule 6 – Amend Entry**

ALPHA-CYPERMETHRIN:

- a) in aqueous preparations containing ~~25~~<sup>30</sup> per cent or less of alpha-cypermethrin; or
- b) in other preparations containing 10 per cent or less of alpha-cypermethrin,

**except** when included in Schedule 5.

The applicant's reasons for the request are:

- The proposed product is a suspension concentrate formulation containing alpha-cypermethrin at 300 g/L (30%). It has low oral, dermal and inhalational toxicity. It is a moderate eye irritant, non-irritant to skin and is unlikely to be a skin sensitiser.
- Based on the low toxicity and non-corrosive properties, the proposed product should be less than Schedule 7.
- A Schedule 6 entry is appropriate as the toxicity fits the criteria of acute inhalation LC<sub>50</sub> between 500–3000 mg/m<sup>3</sup>.
- The toxicity of the product is low enough to warrant an entry in Schedule 5, considering the acute inhalational LC<sub>50</sub> was at the maximum attainable concentration.
- This recommendation is based on the acute toxicity data provided by the applicant and also data provided for the 25% product previously considered by the Committee (NDPSC November 2000).
- Other synthetic pyrethroids included in Schedules 5 or 6 include transfluthrin, permethrin, deltamethrin, esfenvalerate and metafluthrin.
- The product is for commercial agricultural use only.

#### *Current scheduling status*

Alpha-cypermethrin is currently listed in Schedules 5, 6 and 7 and is cross-referenced in the Index to cypermethrin as follows:

##### **Schedule 7**

ALPHA-CYPERMETHRIN **except** when included in Schedule 5 or 6.

##### **Schedule 6**

ALPHA-CYPERMETHRIN:

- a) in aqueous preparations containing 25 per cent or less of alpha-cypermethrin; or

b) in other preparations containing 10 per cent or less of alpha-cypermethrin, **except** when included in Schedule 5.

#### **Schedule 5**

ALPHA-CYPERMETHRIN:

- a) in aqueous preparations containing 3 per cent or less of alpha-cypermethrin; or
- b) in other preparations containing 1.5 per cent or less of alpha-cypermethrin.

#### *Scheduling of CYPERMETHRIN:*

#### **Schedule 6**

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

#### **Schedule 5**

CYPERMETHRIN in preparations containing 10 per cent or less of cypermethrin.

#### **Index**

#### **CYPERMETHRIN**

cross reference: ALPHA-CYPERMETHRIN AND BETA-CYPERMETHRIN, ZETA-CYPERMETHRIN

Schedule 6

Schedule 5

#### *Scheduling of BETA-CYPERMETHRIN*

#### **Schedule 6**

BETA-CYPERMETHRIN.

#### *Scheduling of ZETA-CYPERMETHRIN*

#### **Schedule 6**

ZETA-CYPERMETHRIN in preparations containing 10 per cent or less of zeta-cypermethrin.

#### **Schedule 7**

ZETA-CYPERMETHRIN **except** when included in Schedule 6.

#### ***Relevant scheduling history***

In November 1994, the National Drugs and Poisons Schedule Committee (NDPSC) created new entries for alpha-cypermethrin in Schedule 6 and 7 of the Poisons Standard, with a general cut-off in Schedule 6 of 10%.

In February 1998, the NDPSC decided to down-schedule alpha-cypermethrin to Schedule 5, with a general cut-off of 1.5%, irrespective of formulation. Although alpha-cypermethrin has greater toxicity when it is formulated in oil rather than aqueous suspensions, the committee considered that the 1.5% cut-off provides a reasonable safety factor.

In May 1999, the NDPSC decided that the Schedule 5 cut-off could be increased from 1.5% to 3% for aqueous formulations. The committee did not support an increase in the cut-off for formulations in oil.



In November 1999, the NDPSC made an amendment to the Schedule 5 entry for alpha-cypermethrin. The entry content was changed from alpha-cypermethrin to alpha-cypermethrin.

In November 2000, the NDPSC decided amend the Schedule 6 entry to its current cut-offs.

In June 2003, the NDPSC made a minor editorial amendment to the Schedule 6 entry, that did not alter its meaning or cut-offs, to its current entry.

### ***Australian regulatory information***

Alpha-cypermethrin is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#). Alpha-cypermethrin is not an excipient or active in any medicines on the [ARTG](#).

A search of the [Database of Adverse Events Notifications \(DAEN\)](#) database did not reveal any adverse events or safety issues for alpha-cypermethrin from 1 January 1971 to 17 May 2017.

Eighty five (85) registered or approved insecticide, herbicide, vertebrate poison and parasiticide products were found on the APVMA's PubCRIS database.

### ***International regulations***

#### *United States of America (USA)*

Alpha-cypermethrin was registered for use in the USA in January 2013 as an insecticide.

#### *EU/ECHA*

- [1.alpha.(S\*),3.alpha.]-(.alpha.)-cyano-(3-phenoxyphenyl)methyl3-(2,2-dichlor-oethenyl)-2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylate (alpha-Cypermethrin).
- EC/List no.: 614-054-3.
- Hazard classification and labelling: *Danger!* According to the classification provided by companies to ECHA in CLP notifications this substance is toxic if swallowed, is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, may cause damage to organs through prolonged or repeated exposure, is harmful if inhaled and may cause respiratory irritation.
- Alpha-cypermethrin has been found in the following regulatory activities:
  - The Biocidal Products Committee (BPC) has issued the following opinions on active substance approval:

Active substance	Product type (PT)	BPC opinion	Date of opinion
Alpha-cypermethrin	PT 18	<a href="#">Opinion</a>	17/6/2014

- [Summary of Classification and Labelling for alpha-cypermethrin](#).
- [Import Notifications for alpha-cypermethrin](#).
- [Annex III inventory for alpha-cypermethrin](#).
- [Pre-registered substances for alpha-cypermethrin](#).

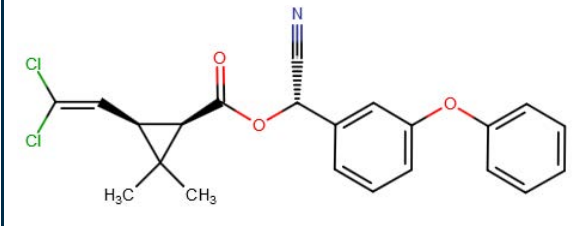
#### *New Zealand*

- [Alpha-cypermethrin](#) approval number: HSR003293.

- Synonyms: (+/-)-cis-cypermethrin.

### Substance summary

**Table 3.3.1: Chemical information for alpha-cypermethrin**

Property	Alpha-cypermethrin
CAS name	( <i>R</i> )-cyano(3-phenoxyphenyl)methyl (1 <i>S</i> ,3 <i>S</i> )- <i>rel</i> -3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate;  Note: Cypermethrin is a racemic mixture of 8 enantiomers. Alpha-cypermethrin consists of two of the <i>cis</i> isomers (i.e. alpha-cypermethrin constitutes 25% of technical cypermethrin, namely the 1- <i>R</i> <i>cis</i> <i>S</i> and 1- <i>S</i> <i>cis</i> <i>R</i> isomers)
CAS number	67375-30-8
Chemical structure	
Molecular formula	C <sub>22</sub> H <sub>19</sub> Cl <sub>2</sub> NO <sub>3</sub>
Molecular weight	416.3 g/mol
IUPAC and/or common and/or other names	Alphamethrin; IUPAC names: 1) racemate comprising ( <i>R</i> )- α -cyano-3-phenoxybenzyl (1 <i>S</i> ,3 <i>S</i> )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and ( <i>S</i> )- α -cyano-3-phenoxybenzyl (1 <i>R</i> ,3 <i>R</i> )-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; or 2) racemate comprising ( <i>R</i> )- α -cyano-3-phenoxybenzyl (1 <i>S</i> )- <i>cis</i> -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and ( <i>S</i> )- α -cyano-3-phenoxybenzyl (1 <i>R</i> )- <i>cis</i> -3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

The following information was extracted from the AVPMA human health risk assessment (HHRA) technical report for the toxicology of alpha-cypermethrin.

**Table 3.3.2: Acute toxicity end-points for alpha-cypermethrin**

Toxicity	Species	Alpha-cypermethrin and product	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	> 5000 mg/kg bw for 50% aqueous suspension >2000 mg/kg bw for product	N/A Schedule 5

Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Mouse	> 100 mg/kg bw alpha-cypermethrin (concentration unknown)	Schedule 7
	Rat	> 2000 mg/kg bw for product	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Not given	> 400 mg/m <sup>3</sup> (30% silica powder dust)	Schedule 7
	Rat	> 1150 mg/m <sup>3</sup> (4h) (maximum attainable concentration) for the product	Schedule 6
Skin irritation	Rabbit	Slight for active constituent	Schedule 5
		Nil for product	N/A
Eye irritation	Rabbit	Slight for active constituent	Schedule 5
		Moderate for product	Schedule 5
Skin sensitisation (Buehler)	Guinea pig	Negative for active constituent	N/A
		Negative for product	N/A

### *Acute toxicity*

The acute toxicity profile of alpha-cypermethrin varies with vehicle and/or species. The acute oral toxicity in rats ranges from low in 50% aqueous suspension (LD<sub>50</sub> > 5000 mg/kg bw) to high in 5% corn oil (LD<sub>50</sub> = 79 mg/kg bw). The comparable LD<sub>50</sub> values for mice are 798 mg/kg bw (50% aqueous suspension) and 35 mg/kg bw (5% corn oil). The major sign of toxicity was clonic convulsions. An acute dermal toxicity study in mice gave an LD<sub>50</sub> > 100 mg/kg bw. There is one acute inhalational LC<sub>50</sub> value for alpha-cypermethrin of > 400 mg/m<sup>3</sup> which is based on a study using a 30% silica powder dust. Based on the acute toxicity studies with the proposed product, which contains 30% alpha-cypermethrin, the product has low acute oral, dermal and inhalation toxicity.

### *Skin irritation*

Alpha-cypermethrin is a slight skin irritant in rabbits. Based on an acute dermal irritation study, the proposed product is not a skin irritant.

### *Eye irritation*

Alpha-cypermethrin is a slight eye irritant in rabbits. Based on available data, the proposed product is a moderate eye irritant:

Three female rabbits were administered the proposed product by ocular instillation. Ocular irritation was scored according to the Draize scale and compared with the untreated eye for each animal at 1, 24, 48, 72, 96 hours and 5, 6 and 7 days after treatment. All three animals exhibited ocular lesions (conjunctival oedema, redness and corneal opacity) in the treated eye from 1h till day 6 post instillation. These lesions were reversible and comparable to the untreated eye on day 7. Thereafter all animals appeared healthy and gained body weight during the study. No signs of gross toxicity or behavioural changes were observed in any of the animals. Under the study conditions described, with corneal opacity for 6 days that was reversible on day 7, the proposed product is a moderate eye irritant.

### *Sensitisation*

Alpha-cypermethrin did not cause skin sensitisation in guinea pigs. Based on a guideline-compliant Buehler study, the proposed product is not a skin sensitiser.

### *Repeat-dose toxicity*

In 4- to 13-week dietary studies in rats and dogs, neurotoxicity was the primary effect. Clinical signs of toxicity included ataxia, body tremors, agitation, and abnormal gait. Histopathological changes were seen in the liver (glycogenic vacuolation of parenchyma), and axonal degeneration of the sciatic nerve. There was decreased bodyweight gain, and increased liver and kidney weights. The NOAEL was 6.4 mg/kg bw/d in rats and 4.7 mg/kg bw/d dogs.

### *Genotoxicity*

Alpha-cypermethrin was not mutagenic in bacteria or yeast. It did not break DNA or induce chromosome damage in *in vivo* assays in rat and was not clastogenic in the rat liver cells *in vitro*.

### *Reproduction and developmental toxicity*

There are no long term repeat dose, reproduction or developmental studies conducted using alpha-cypermethrin that have been previously evaluated.

### *Observation in humans*

Human volunteers participated in two oral dose-excretion studies using alpha-cypermethrin. On two occasions, two volunteers per dose received a single oral dose of 0.25, 0.5 or 0.75 mg alpha-cypermethrin in corn oil (as a gelatine capsule) with 24-h urine collections. Urinary excretion was rapid, with 43% - 49% of the dose excreted within the first 24 h, 1-5% on Day 2 and 1-7% on Day 6.

### *Public exposure*

The product is not intended for home garden use. Dermal absorption of alpha-cypermethrin is low. Public exposure to the product is unlikely to occur.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACCS advice to the delegate***

The committee recommended that the Schedule 6 entry for alpha-cypermethrin be amended as follows:

#### **Schedule 6 – Amend Entry**

ALPHA-CYPERMETHRIN:

- a) in aqueous preparations containing ~~25~~<sup>30</sup> per cent or less of alpha-cypermethrin; or
- b) in other preparations containing 10 per cent or less of alpha-cypermethrin,

**except** when included in Schedule 5.

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

---

- a) the risks and benefits of the use of a substance:
- Nil.
- b) the purposes for which a substance is to be used and the extent of use of a substance:
- Nil.
- c) the toxicity of a substance:
- The acute oral and inhalation toxicity at 30% of alpha-cypermethrin is consistent with Schedule 6 criteria (SPF 2015). These hazards can be controlled with appropriate labels and handling protocols.
- d) the dosage, formulation, labelling, packaging and presentation of a substance:
- alpha-Cypermethrin is intended for agricultural use and not for domestic use.
- e) the potential for abuse of a substance:
- Nil.
- f) any other matters that the Secretary considers necessary to protect public health:
- This is an extension of the current Schedule 6 entry, which is consistent with the toxicity data.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

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

### ***Delegate's interim decision***

The delegate's interim decision is to amend the Schedule 6 entry for alpha-cypermethrin by increasing the permitted concentration from 25% to 30% in aqueous preparations. The proposed Schedule entry is:

#### **Schedule 6 – Amend Entry**

ALPHA-CYPERMETHRIN:

- a) in aqueous preparations containing 30 per cent or less of alpha-cypermethrin; or
- b) in other preparations containing 10 per cent or less of alpha-cypermethrin,

**except** when included in Schedule 5.

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (c) the toxicity of the 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 are the following:

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

- Nil.

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

- Nil.

c) the toxicity of a substance:

- The acute oral and inhalation toxicity at 30% of alpha-cypermethrin is consistent with Schedule 6 criteria (SPF 2015). These hazards can be controlled with appropriate labels and handling protocols.

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

- alpha-Cypermethrin is intended for agricultural use and not for domestic use.

e) the potential for abuse of a substance:

- Nil.

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

- This is an extension of the current Schedule 6 entry, which is consistent with the toxicity data.

### 3.4 Silver Oxide

#### *Referred scheduling proposal*

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to consider silver oxide for scheduling in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### *Scheduling application*

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

##### **Appendix B – New Entry**

##### **SILVER OXIDE**

The applicant's reasons for the request are:

- Data from (soluble) silver compounds were used to establish a toxicology profile for this silver salt, mainly on silver and silver nitrate which are listed in the Poisons Standard.
- However, not only is the silver concentration in the proposed product below the Poisons Standard cut-offs for the scheduling of both silver and silver nitrate, but both the presentation/packaging and use pattern restricts hazard.
- The product's presentation/packaging restricts hazard and the product's use pattern (spa pool sanitiser) restricts hazard.
- There is no identified public health risk for silver oxide.

The majority of studies used to establish a toxicological profile for silver oxide (soluble silver) were conducted with silver nitrate that is included on the APVMA list of [actives not requiring evaluation](#). Therefore, it is recommended that consideration is given to include silver oxide on this list.

### ***Current scheduling status and relevant scheduling history***

SILVER OXIDE is not specifically scheduled.

Related silver scheduling:

#### **Schedule 6**

SILVER NITRATE **except:**

- a) when included in or expressly excluded from Schedule 2; or
- b) in preparations containing 1 per cent or less of silver.

#### **Schedule 2**

SILVER for therapeutic use **except:**

- a) in solutions for human oral use containing 0.3 per cent or less of silver when compliant with the requirements of the Required Advisory Statements for Medicine Labels; or
- b) in other preparations containing 1 per cent or less of silver.

#### **Appendix E, Part 2**

Silver salts: A, E2.

Silver oxide is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

### ***Australian regulatory information***

Silver oxide is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#).

Silver oxide is not an excipient or active ingredient in any medicines on the [ARTG](#).

### ***International regulations***

#### ***European Union***

[Silver substances currently approved for use in Europe](#) include silver oxide, silver chloride, metallic silver, silver citrate and silver nitrate. Functions of these silver containing substances vary from deodorising and antimicrobial to preserving and skin conditioning.

Silver oxide is the silver source in cosmetic grade Nolla™ in Europe. Other silver substances such as metallic silver and silver chloride can be used when regulations allow it outside Europe. All approved cosmetic ingredients in Europe can be found on the [database](#) maintained by the European Commission.

#### ***ECHA***

- Disilver oxide. IUPAC name: silver oxide.



- EC/List no.: 243-957-1.
- Trade names: G-58 C and OleMax types.
- Hazard classification and labelling: *Danger!* According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life, with long lasting effects, may cause fire or explosion (strong oxidiser) and causes serious eye damage.
- This substance is manufactured and/or imported in the European Economic Area in 100 - 1 000 tonnes per year. This substance is used in articles by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.
- Consumer Uses: ECHA has no publicly registered data indicating in which chemical products the substance might be used. ECHA has no publicly registered data on the routes by which this substance is most likely to be released to the environment.
- Article service life: Release to the environment of this substance is likely to occur from industrial use: in the production of articles. Other releases to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment). This substance can be found in complex articles, with no release intended: machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines), electrical batteries and accumulators and vehicles. This substance can be found in products with material based on: metal (e.g. cutlery, pots, toys, jewellery).
- Widespread uses by professional workers: ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the types of manufacture using this substance. Release to the environment of this substance is likely to occur from industrial use: in the production of articles.
- Formulation or re-packing: ECHA has no publicly registered data indicating whether or in which chemical products the substance might be used. Release to the environment of this substance is likely to occur from industrial use: formulation of mixtures.
- Uses at industrial sites: This substance is used in the following products: biocides (e.g. disinfectants, pest control products), laboratory chemicals, water treatment chemicals and pH regulators and water treatment products. This substance is used for the manufacture of: chemicals, fabricated metal products and electrical, electronic and optical equipment. Release to the environment of this substance is likely to occur from industrial use: in the production of articles.
- Manufacture: Release to the environment of this substance is likely to occur from industrial use: manufacturing of the substance.

#### *United States of America (USA)*

[Code of Federal Regulations](#), Sec. 310.548 Drug products containing colloidal silver ingredients or silver salts offered over the counter (OTC) for the treatment and/or prevention of disease.

Colloidal silver ingredients and silver salts have been marketed in OTC drug products for the treatment and prevention of numerous disease conditions. There are serious and complicating aspects to many of the diseases these silver ingredients purport to treat or prevent. Further, there is a lack of adequate data to establish general recognition of the safety and effectiveness of colloidal silver ingredients or silver salts for OTC use in the treatment or prevention of any disease. These ingredients and salts include, but are not limited to, silver proteins, mild silver protein, strong silver protein, silver, silver ion, silver chloride, silver cyanide, silver iodide, silver oxide, and silver phosphate.

Natural health products ingredients database – homeopathic substance:

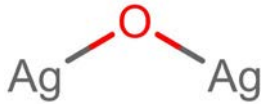
Ingredient	Proper Name(s)	Common Name(s)
<a href="#">EHP Argentum oxydatum</a> (Homeopathic Substance)	<ul style="list-style-type: none"> <li>Argentum oxydatum</li> <li>Oxyde d'argent</li> <li>Silver oxide</li> </ul>	<ul style="list-style-type: none"> <li>Argentum oxydatum</li> <li>Oxyde d'argent</li> <li>Silver oxide</li> </ul>

#### New Zealand

- [Silver oxide](#) approval number: HSR001346.
- Synonyms: disilver oxide.

#### Substance summary

**Table 3.4.1: Chemical information for silver oxide**

Property	Silver oxide
CAS names	Silver oxide
CAS numbers	20667-12-3
Chemical structure	
Molecular formula	Ag <sub>2</sub> O
Molecular weight	231.7 g/mol
IUPAC and/or common and/or other names	Silver monoxide; Argentous oxide; Silver rust InChI: 1S/2Ag.O IUPAC: Silver (I) oxide

The following information was extracted from the AVPMA human health risk assessment (HHRA) technical report for the toxicology of silver oxide.

**Table 3.4.2: Acute toxicity end-points for silver oxide**

Toxicity	Species	[Silver oxide]	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	280 (for ionic silver)	Schedule 6

	Mouse	32 (ionic silver)	
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	-	No data	-
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	-	No data	-
Respiratory irritation	-	Respiratory irritant (>20%)	-
Skin irritation	-	No data	-
Eye irritation	-	No data	-
Skin sensitisation	Guinea pig	Non-sensitiser	N/A

Since no studies were available for silver oxide (the salt source of soluble silver), the toxicological profile for silver oxide was determined using data on soluble silver compounds from published reviews. Many of the studies reported in these reviews were conducted prior to the principles of GLP being established by the OECD in 1978. However, as a toxicological profile was established for registration of the product and not approval of the active constituent, the data that also included information on human exposure to silver compounds were considered to be sufficient for risk assessment purposes.

The majority of studies used to establish a toxicological profile for silver oxide (soluble silver) were conducted with silver nitrate that is included on the APVMA list of [actives not requiring evaluation](#). Therefore, the APVMA recommends that consideration is given to include silver oxide on this list.

Silver oxide is formed in the manufacturing process for the product the proposed product. Silver oxide is present in the proposed product at 1% of which 0.93% is silver. The proposed product is a spa pool product intended for domestic use, whose sanitising effects are due to the gradual release of silver from the silver oxide over time. The product's formulation type, presentation and packaging means that direct user exposure to the product would not be considered to occur under normal conditions of use (i.e. presentation/packaging restricts hazard).

The qualitative determination of exposure and risk undertaken indicates that the acute and repeated risks from swimming in the proposed product treated spa pools are considered to be low to negligible and therefore acceptable (i.e. use pattern restricts hazard).

Silver and silver nitrate that established the toxicology profile are both currently scheduled in the Poisons Standard.

#### *Acute toxicity*

For soluble silver, the oral and dermal absorption in humans was 21% and <1% respectively, and it was of moderate acute oral toxicity in the rat (LD<sub>50</sub> 280 mg/kg bw). No acute dermal or inhalation studies were available. Skin and ocular "burns" have been reported with occupational exposure to silver nitrate, though such findings are likely due to the corrosive effect of nitrate rather than by silver itself. The most frequent abnormal ocular finding in workers was argyrosis which was also observed in rats. Silver was not considered a skin sensitiser. Human and animal data indicate it was a respiratory irritant. The limited systemic findings in rats do not warrant scheduling.

The product the proposed product was estimated to have low acute oral, dermal and inhalation toxicity, moderate skin irritation, severe eye irritation, and neither a skin sensitiser or respiratory irritant. The estimated skin and eye irritant potential were attributed to product constituents other than silver oxide.

### *Mutagenicity; reproduction and developmental toxicity*

*In vitro*, silver was not mutagenic in bacteria but was clastogenic in mammalian cells causing chromosome aberrations and DNA strand breaks. No *in vivo* studies were available. There is no historical evidence of silver having a carcinogenic potential. It was concluded that silver is unlikely to pose a carcinogenic risk to humans. The findings in the one generation study were not considered to provide robust evidence that silver is a reproductive toxicant. Silver was not teratogenic, neurotoxic or immunotoxic in rats.

### *Observation in humans*

The only data reported on silver oxide in the published reviews were for occupational exposure, with co-exposure to silver nitrate also reported to occur. In humans, the main reported effect after long-term inhalation or ingestion to high doses of silver was the development of argyria and/or argyrosis, with the evidence suggesting the pigmentation does not interfere with the normal functioning of organs. Respiratory irritation and argyrosis were reported to occur, along with abdominal pain in one study. However, the limited reporting detail for these studies meant they were not reliable for risk assessment purposes.

### ***Pre-meeting public submissions***

One (1) submission was received for silver oxide that supported the proposal. The main point was:

- Silver oxide is used as a biocide in spa and tool sanitiser products. An entry in Appendix B would be a straightforward way to ensure that there are no unintended effects on the regulatory status of other silver compounds and/or derivatives which may be used in other sectors.

The public submission will be made available on the [TGA website](#).

### ***Summary of ACCS advice to the delegate***

The committee recommended that silver oxide does not require scheduling and should therefore be included in Appendix B, as follows:

#### **Appendix B – New Entry**

#### **SILVER OXIDE**

**Reasons for Entry: b (Use pattern restricts hazard)**

**Areas of Use: 7.14 (Spa/pool sanitiser)**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- Risks: As presented, the benefits of silver oxide are likely to greatly outweigh the risks.
- Benefits: silver oxide reduces bacterial levels in spas.

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

- The use of silver oxide as a spa pool sanitiser will allow for the soluble silver to be dissolved into the spa.
- Minimal exposure to silver is expected.

c) the toxicity of a substance:

- Toxicity of silver oxide is not well characterised.
- The presentation restricts the potential for respiratory irritancy.

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

- Formulation as an integral part of a silicate glass, which is further contained, is the key to the low risk, more than simply the low solubility of silver oxide.
- Silver oxide present in a product for the domestic market is at 1% (<1% silver), allowing for gradual release of silver over time.

e) the potential for abuse of a substance:

- Nil.

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

- There is insufficient data for a Schedule 6 entry.

### ***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)

### ***Delegate's interim decision***

The delegate's interim decision is that silver oxide does not require scheduling and to include it in Appendix B of the Poisons Standard. The proposed decision is:

#### **Appendix B – New Entry**

SILVER OXIDE

Reasons for Entry: b (Use pattern restricts hazard)

Areas of Use: 7.14 (Spa/pool sanitiser)

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

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

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

- Risks: As presented, the benefits of silver oxide are likely to greatly outweigh the risks.
- Benefits: silver oxide reduces bacterial levels in spas.

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

- The use of silver oxide as a spa pool sanitiser will allow for the soluble silver to be dissolved into the spa.
- Minimal exposure to silver is expected.

c) the toxicity of a substance:

- Toxicity of silver oxide is not well characterised.
- The presentation restricts the potential for respiratory irritancy.

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

- Formulation as an integral part of a silicate glass, which is further contained, is the key to the low risk, more than simply the low solubility of silver oxide.
- Silver oxide present in a product for the domestic market is at 1% (<1% silver), allowing for gradual release of silver over time.

e) the potential for abuse of a substance:

- Nil.

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

- There is insufficient data for a Schedule 6 entry.

### 3.5 1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives

#### ***Referred scheduling proposal***

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new entry for 1-deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives in Schedule 6 to restrict the use in cosmetic rinse-off and household cleaning preparations in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### ***Scheduling application***

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

#### **Schedule 6 – New Entry**

#### **1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-C10-16 ACYL DERIVATIVES **except:****

- a) in cosmetic rinse-off preparations containing 7 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N-C10-16 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 12 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives when labelled with the following statement:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER.

#### Appendix E, Part 2 – New Entry

Standard Statement: E1 (If in eyes wash out immediately with water).

#### Appendix F, Part 3 – New Entry

Warning Statement: 79 (Will irritate eyes).

Safety Direction: 1 (Avoid contact with eyes).

The applicant's reasons for the request are:

- 1-Deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives cause serious eye damage in *in vivo* tests with a GHS hazard classification of serious eye damage/eye irritation (Category 1) and a hazard statement of H318 – Causes serious eye damage.
- 1-Deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives are used as a surfactant in rinse-off cosmetics at a concentration ≤ 7% and household cleaning products at a concentration ≤ 12%. Widespread and repeated public exposure is expected through the use of products containing the chemical. 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 1-deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives conform to the Scheduling Policy Framework factors for Schedule 6, specifically severe eye irritation in rabbits (corneal opacity not reversible in 21 days concurrent with conjunctival effects).
- Irreversible eye damage or severe eye irritation can occur when consumers use products containing relatively high concentrations of 1-deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives, especially hair/skin cleansing products that may come into direct contact with the eyes.
- Reasonably foreseeable harm to users can be reduced through strong label warnings and extensive safety directions. Setting a concentration cut-off for 1-deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives can protect consumers from serious eye damage.
- An analogue of 1-deoxy-1-(methylamino)- D -glucitol *N*-C10-16 acyl derivatives (1-deoxy-1-(methylamino)- D -glucitol *N*-coco acyl derivatives, CAS No. 1591783-13-9), having very similar hazard, use and risk profiles, was recently scheduled in Schedule 6 of the Poisons Standard.

#### Current scheduling status

1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives is not currently specifically scheduled in the [Poisons Standard](#).

1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives, an analogue of 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives, was recently considered for scheduling at the November 2016 Advisory Committee on Chemicals Scheduling (ACCS). The [delegate's final decision for 1-deoxy-1-\(methylamino\)-D-glucitol \*N\*-coco acyl derivatives](#), to be implemented on 1 February 2018, was to create a new Schedule 6 entry as follows:

#### Schedule 6

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

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- 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

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

### Appendix F, Part 3 – New Entry

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

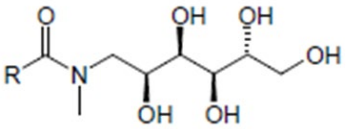
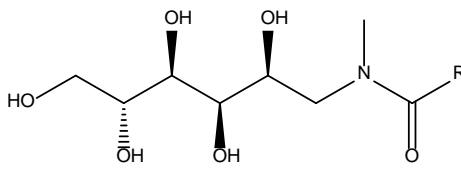
cross reference: cocoyl methyl glucamide

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

Due to the similarity in chemical structure, hazard, use and risk profiles 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives is captured by the above Schedule 6 entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives :

1-deoxy-1-(methylamino)-D-glucitol <i>N</i> -C10-16 acyl derivatives Scheduling under consideration	1-deoxy-1-(methylamino)-D-glucitol <i>N</i> -coco acyl derivatives Schedule 6
 <p>Major components: R = C<sub>11</sub>H<sub>23</sub> (<i>lauroyl methyl glucamide</i>) R = C<sub>13</sub>H<sub>27</sub> (<i>myristoyl methyl glucamide</i>)</p>	 <p>Where R = C7-C17 alkyl group or C17 alkenyl group</p>

### Relevant scheduling history

1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives has not been previously considered for scheduling. A scheduling history is therefore not available for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives.

An analogue of 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives, 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives has been previously considered for scheduling as follows:

### Scheduling history of 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives

At the November 2016 ACCS meeting the committee considered a proposal to schedule 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives. The committee recommended that based on the use of 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives as a surfactant, its severe eye irritancy and risk of spray products containing 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives entering the eye, that 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives be scheduled with exemptions and cut-off concentrations in cosmetic rinse-off preparations and household cleaning products. The delegate agreed however noting that a longer implementation time of 1 February 2018 would be required to allow for labelling changes and/or reformulation.

### Australian regulatory information

1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives (lauroyl/myristoyl methyl glucamide) does not appear to be in any products on the ARTG.

1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives (lauroyl/myristoyl methyl glucamide) is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#).

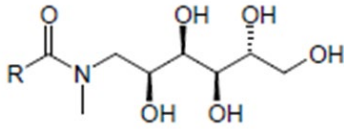
### International regulations

The chemical was registered under REACH as of 6 July 2012. The registration dossier was updated on 17 April 2017, following compliance checks by ECHA.

No known international restrictions or regulations have been identified by the applicant or the Secretariat.

### Substance summary

**Table 3.5.1: Chemical information for 1-deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives**

Property	1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives
CAS number	173145-38-5
Chemical structure	 <p>Major components: R = C<sub>11</sub>H<sub>23</sub> (lauroyl methyl glucamide) R = C<sub>13</sub>H<sub>27</sub> (myristoyl methyl glucamide)</p>
IUPAC, CAS and/or common and/or other names	D-glucitol, 1-deoxy-1-(methylamino)-, N-C10-16 acyl derivatives (CAS); Lauroyl/myristoyl methyl glucamide (INCI) C12-14 linear glucose amide; Lauryl methyl glucamide.

The following information was extracted from the [NICNAS assessment report for C12-14 Linear Glucose Amide](#) and the [NICNAS Existing Chemical secondary notification assessment report for D-glucitol, 1-deoxy-1-\(methylamino\)-, N-C10-16 acyl derivatives](#).

**Table 3.5.2: Acute toxicity end-points for 1-deoxy-1-(methylamino)-D-glucitol N-C10-16 acyls**

Toxicity	Species	1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	> 2000	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rabbit	> 2000	Schedule 5
Acute inhalation toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	No data provided	No data provided	-
Skin irritation (human three application patch test)	Rabbit	Slight irritant	Schedule 5
	Human		
Eye irritation	Rabbit	Severely irritating	Schedule 6
Skin sensitisation (Buehler)	Guinea pig	Not skin sensitising	Schedule 5

#### Acute toxicity

Based on the studies provided, 1-deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives has a low acute oral and dermal toxicity (LD<sub>50</sub> > 2000 mg/kg bw) in rats.

#### Skin irritation

1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives is slightly irritating to rabbit skin, with Grade 1 erythema (two of three animals) and Grade 1 oedema (one of three animals) persisting for up to 7 days. The results do not warrant classification of the substance under the GHS.

#### Eye irritation

1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives is a severe irritant to rabbit eyes in pure form, with vascularisation of the cornea observed in one out of the three animals tested. The irritation scores in this test could not be directly assessed against the GHS as the quantity instilled in the eyes was less than 10 mg, rather than the 100 mg required by the relevant Organisation for Economic Co-operation and Development (OECD) test guideline. The irritation scores were below the level for classification as an eye irritant, but instillation of larger quantities may have resulted in higher scores. Even at the lower quantity, the irritation was persistent, with effects seen in all animals at 4 days, and persisting up to 35 days in one animal. The results warrant the following classification of the substance under the GHS:

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

### *Sensitisation*

1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives was not a skin sensitiser in guinea pigs using a modified Buehler test.

### *Repeat-dose toxicity*

Based on the available information from studies in rats, repeated oral exposure to the substance is not considered to cause serious damage to health.

- In a 28-day oral study in rats, a NOAEL of 100 mg/kg bw/day was established. At doses of 500 and 1000 mg/kg bw/day, a number of histological changes to the stomach lining were observed. Reduced food consumption and decreased bodyweight were also noted, along with a number of clinical chemistry changes that the study authors attributed to the poor nutritional status of these animals. Twelve of the twenty rats receiving 1000 mg/kg bw/day died or were sacrificed *in extremis* during the study. At the higher doses, breathing difficulties were also observed.
- In a 13-week oral study in rats, breathing problems were observed in animals treated with 50 mg/kg bw/day and above. Clinical chemistry and haematology parameters were changed in animals treated with 200 and 500 mg/kg bw/day. These changes were considered to be due to the poor general condition of the animals. Six out of twenty animals treated with 500 mg/kg bw/day died of treatment-related causes during the study. No macroscopic or microscopic changes could be found during necropsy to explain the reasons for the deaths. On the basis of increased mortality and morbidity at 500 mg/kg bw/day, the study authors concluded that the NOAEL was 200 mg/kg bw/day in this study, as all findings at this dose were slight and there were no changes in blood or urinalysis parameters indicative of toxicity. However, based on clinical signs and the slight, transient effects on body weight gain at 200 mg/kg bw/day, a NOEL of 50 mg/kg bw/day was established.

### *Mutagenicity*

1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives tested negative in two *in vitro* mutagenicity tests (*Salmonella typhimurium* reverse mutation assay and mouse lymphoma forward mutation assay) in the presence and absence of S9 metabolic activation. Positive results were observed in an *in vitro* study of chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of metabolic activation, although the study authors concluded that the results were not biologically significant because of lack of reproducibility in repeat tests and because the values were within historical control ranges. This conclusion was supported by the negative genotoxicity results in an *in vivo* cytogenicity study in rat bone marrow cells.

### *Carcinogenicity*

No information was provided.

### *Reproduction and developmental toxicity*

In a one generation study in rats, 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives was not toxic to fertility or development. It caused adverse effects in parental animals on prolonged exposure to 350 mg/kg bw/day (reduction in body weight gains and in feed consumption in females).

In a developmental toxicity study, 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives did not cause developmental toxicity in rats at a dose where maternal toxicity was observed. The NOEL for developmental toxicity was determined to be 363 mg/kg bw/day (the highest dose tested) while the NOAEL for maternal toxicity was found to be 150 mg/kg bw/day based on decreased bodyweight gain at the higher dose.

### *Observation in humans*

A three application patch test in human volunteers showed that 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives was a mild skin irritant.

Several skin irritation and sensitisation studies in humans have been performed using the C12 glucose amide component of 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives and formulations containing this component. However, the full details the formulation studies were not available. Consistent with the results of the animal studies for the substance, the C12 component was found to be a slight skin irritant under the conditions of the tests but was not a skin sensitiser.

### *Public exposure*

The public exposure to 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives 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 7% concentration in rinse-off cosmetics for skin and hair cleansing and at up to 12% concentration in household cleaning products. As 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives is classified as a Category 1 severe eye irritant at concentrations at or above 3%, without label warnings and appropriate directions, use of 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives in consumer products at or above 3% could result in severe eye irritation to users. Setting a concentration cut-off for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives used in cosmetics and household products, and providing users with labelling and first aid information could protect consumers.

### ***Pre-meeting public submissions***

Two (2) pre-meeting submission was received, one (1) that opposed the scheduling proposal for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives and one (1) that did not state their position.

#### *The main points were:*

- Scheduling of individual surfactants through the chemical scheduling process is out of step with international requirements for these substances and is unnecessary due to the well-established history of safe use of surfactant based products.
- Recent advice from the committee on other surfactants (docusate sodium, sodium  $\alpha$ -olefin sulfonates and sodium alkyl sulfates) indicate that “*there is no evidence of a public health risk*” from these kinds of substances.
- Support of the committee’s recent advice that a review into the scheduling of all surfactants (including this substance) should take place. Further consultation with industry is needed should a review take place.
- This substance is not entered in the TGA eBS ingredients list, nor is it entered in the TGA Permitted Ingredients List. It is therefore assumed that the scheduling proposal will not impact therapeutic goods. Should any inadvertent impact be revealed, we would like to provide comment during the public consultation on the interim decision.

The public submissions will be made available on the [TGA website](#).

### ***Summary of ACCS advice to the delegate***

The committee recommended that the schedule 6 and index entries for the 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives be amended as follows:

#### **Schedule 6 – Amend 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-coeo~~ acyl derivatives when labelled with a **warning statement** to the following **effect statement**:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or

- b) In household cleaning preparations, other than those intended to be sprayed, containing ~~10~~**12** per cent or less of 1-deoxy-1-(methylamino)-D-glucitol ~~N-coeo~~ acyl derivatives when labelled with a **warning statement** to the following **effect statement**:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER.

**Index – Amend Entry**

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

**cross-reference: COCOYL METHYL GLUCAMIDE, LAUROYL METHYL GLUCAMIDE, MYRISTOYL METHYL GLUCAMIDE**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date. It should be noted that the new Schedule 6 entry for delegate's final decision on 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is to be implemented on 1 February 2018.

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

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

- Risks: 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives is a severe eye irritant and a skin irritant. This is a common hazard for all surfactants including soap and this hazard/risk is well understood by the public.
- Benefits: surfactants as a group are useful, as they increase miscibility of hydrophilic and hydrophobic substances.

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

- The applicant identified that 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives are potentially in widespread use in cosmetics and domestic (household cleaning) products.

c) the toxicity of a substance:

- 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives are a severe eye irritant and skin irritant.

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

- The current known formulations are up to 8% concentration in cosmetics and 12% in household cleaning products.
- Currently, products with this chemical in the formulation would be labelled, packaged and presented appropriately for a cosmetic product or a household cleaning product, i.e. small packaging with use instructions as appropriate.



e) the potential for abuse of a substance:

- Nil.

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

- The primary intent of the existing entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives is to provide label directions that the eyes should be washed if the chemical gets in the eye. This has the effect of scheduling the chemical at any concentration in spray cleaners.
- There is ongoing research with the aim to provide surfactants for use in cosmetics and household products that have the lowest possible irritancy and sensitising potential in order to improve public health protection and ecological impact.

### ***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 not specifically list 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives as it is captured by the Schedule 6 entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives, which is to be implemented on 1 February 2018, and to amend the 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives by removing "*coco*" to capture similar substances. The proposed schedule entry is:

#### **Schedule 6 – Amend Entry**

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

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

IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or

- b) in household cleaning preparations, other than those intended to be sprayed, containing 12 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-acyl derivatives when labelled with a warning statement to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER.

#### **Index – Amend Entry**

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

cross-reference: COCOYL METHYL GLUCAMIDE, LAUROYL METHYL GLUCAMIDE, MYRISTOYL METHYL GLUCAMIDE

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.



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

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

- Risks: 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives are a severe eye irritant and a skin irritant. This is a common hazard for all surfactants including soap and this hazard/risk is well understood by the public.
- Benefits: surfactants as a group are useful, as they increase miscibility of hydrophilic and hydrophobic substances.

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

- The applicant identified that 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives are potentially in widespread use in cosmetics and domestic (household cleaning) products.

c) *the toxicity of a substance:*

- 1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives are a severe eye irritant and skin irritant.

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

- The current known formulations are up to 8% concentration in cosmetics and 12% in household cleaning products.
- Currently, products with 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives in the formulation would be labelled, packaged and presented appropriately for a cosmetic product or a household cleaning product, i.e. small packaging with use instructions as appropriate.

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

- Nil.

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

- The primary intent of the existing entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is to provide label directions that the eyes should be washed if the chemical gets in the eye. This has the effect of scheduling the chemical at any concentration in spray cleaners.
- There is ongoing research with the aim to provide surfactants for use in cosmetics and household products that have the lowest possible irritancy and sensitising potential in order to improve public health protection and ecological impact.

## 3.6 Phenyl methyl pyrazolone

### *Referred scheduling proposal*

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new entry for phenyl methyl pyrazolone in Schedule 6 or 5 with an exemption cut-off of 0.25% in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

## ***Scheduling application***

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

### **Schedule 5 OR 6 – New Entry**

PHENYL METHYL PYRAZOLONE **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 0.25 per cent or less after mixing for use 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**

#### **PHENYL METHYL PYRAZOLONE**

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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

### **Appendix F, Part 3 – New Entry**

#### **PHENYL METHYL PYRAZOLONE**

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

Safety Directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

The applicant's reasons for the request are:

- Phenyl methyl pyrazolone is used in cosmetic products in Australia (in permanent and semi-permanent hair dyes).
- Phenyl methyl pyrazolone is used in cosmetic products overseas at concentrations up to 0.25%.
- Phenyl methyl pyrazolone is a skin sensitiser in animal studies. There is no epidemiological data showing cases of sensitisation in humans.
- Restrictions on the cosmetic use of phenyl methyl pyrazolone overseas (EU, NZ and ASEAN) are considered appropriate to mitigate the risk.

## ***Current scheduling status and relevant scheduling history***

Phenyl methyl pyrazolone is not currently scheduled in the current [Poisons Standard](#). Phenyl methyl pyrazolone has not been previously considered for scheduling. Therefore, a scheduling history is not available for phenyl methyl pyrazolone.

Phenyl methyl pyrazolone shares some structural similarity with aminophenazone (amidopyrine), which is in Schedule 10 for human therapeutic use and Schedule 4 for the treatment of animals as follows:

### **Schedule 10**

AMINOPHENAZONE (amidopyrine) and its derivatives for human therapeutic use.

### **Schedule 4**

AMINOPHENAZONE (amidopyrine) and derivatives for the treatment of animals.

### **Australian regulatory information**

Phenyl methyl pyrazolone does not appear to be in any products listed on the ARTG.

Phenyl methyl pyrazolone is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#).

### **International regulations**

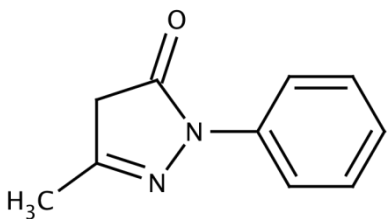
In New Zealand and the Association of Southeast Asian Nations, phenyl methyl pyrazolone may be used in oxidative hair dyes at a maximum concentration applied to hair of 0.25%, after mixing under oxidative conditions.

In the European Union (EU) (Annex III / Cosmetics Regulation (EC) No. 1223/2009 no. 228), the current restriction for phenyl methyl pyrazolone is as follows:

- Product type, body parts: 'Oxidising colouring agents for hair dyeing'
- Maximum concentration in ready for use preparations: '0.5%'
- Other: 'In combination with hydrogen peroxide the maximum use concentration upon application is 0.25 % Not to be used after 31.12.2009'.<sup>57</sup>

### **Substance summary**

**Table 3.6.1: Chemical information for phenyl methyl pyrazolone**

Property	Phenyl methyl pyrazolone
CAS number	89-25-8
Chemical structure	
Molecular formula	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O
Molecule weight	174.2 g/mol
IUPAC, CAS and/or common and/or other names	Phenyl methyl pyrazolone (INCI); 3H-pyrazol-3-one, 2,4-dihydro-5-methyl-2-phenyl- (CAS); 5-methyl-2-phenyl-4H-pyrazol-3-one (IUPAC); 3H-pyrazol-3-one, 2,4-dihydro-5-methyl-2-phenyl- (AICS); 3-methyl-1-

<sup>57</sup> [Official Journal of the European Union, Regulations \(EC\) No. 1221/2009, 1222/2009 and 1223/2009.](#)

	phenyl-5-pyrazolone (EINECS); Evaravone; Radicut; norphenazone; norantipyrine; MCI 186
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The following information was extracted from the [NICNAS IMAP Human Health Tier II assessment report for 3H-Pyrazol-3-one, 2,4-dihydro-5-methyl-2-phenyl-](#).

**Table 3.6.2: Acute toxicity end-points for phenyl methyl pyrazolone**

Toxicity	Species	Phenyl methyl pyrazolone	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat (Sprague Dawley)	>2000 mg/kg bw	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	No data available	N/A	N/A
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	No data available	N/A	N/A
Skin irritation	Rabbit (New Zealand White)	Slightly irritating	Schedule 5
Eye irritation	Rabbit (New Zealand White)	Not irritating	N/A
Skin sensitisation (local lymph node assay (LLNA))	Mouse (CBA) Mouse (CBA)	Strong (EC3 = 1%) Moderate (EC3 >2.5%)	Schedule 6

#### *Acute toxicity*

Phenyl methyl pyrazolone has low acute oral toxicity:

- Phenyl methyl pyrazolone is not acutely toxic. The median lethal dose (LD<sub>50</sub>) was consistently above 2000 mg/kg. 4 different vehicles were used. The repeated daily oral administration of Phenyl methyl pyrazolone to rats for 13 weeks at 20, 100, and 500 mg/kg/day was mainly associated with changes indicative of regenerative haemolytic anaemia at 500 mg/kg/day. Clinical signs attributed to Phenyl methyl pyrazolone but related to the mode of administration were observed at 100 mg/kg/day and higher. In males, the exposure of 100 mg/kg/day resulted in lower blood levels of glucose. The NOAEL was determined to be 100 mg/kg/day. The NOEL was set at 20 mg/kg bw. Phenyl methyl pyrazolone had no teratogenic potential. Maternal toxicity was seen at 1000 mg/kg/day. The NOAEL of maternal and developmental toxicity was 200 mg/kg/day (SCCS 2006).

No data are available for other routes of exposure.

#### *Skin and eye irritation*

Phenyl methyl pyrazolone has been reported to slightly irritate the skin but to have no effect on the eyes. The limited data available are insufficient to warrant hazard classification for skin or eye irritation.

Norantipyrene (Phenyl methyl pyrazolone), at a concentration of 1 %, showed no signs of irritation (SCCS 2006).

#### *Sensitisation*

Phenyl methyl pyrazolone is a moderate to strong skin sensitiser based on the results of two local lymph node assays (LLNA) on CBA mice, indicating an estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) of 1% in one test and >2.5% in the other test.

- 'The sensitisation test was carried out inadequately. In the 28-day study with rats, effects were still found in the 1000 mg/kg bw group. The dose level without effect is 200 mg/kg bw' (SCCS 2006).

#### *Repeat-dose toxicity*

Phenyl methyl pyrazolone is not expected to be harmful to health following repeated oral exposure. A no observed adverse effect level (NOAEL) of 100 mg/kg bw/day for Sprague-Dawley rats was determined in a guideline subchronic toxicity study. No data are available for other routes of exposure.

#### *Genotoxicity*

Based on the weight of evidence from the available *in vitro* and *in vivo* studies conducted in accordance with OECD test guidelines, phenyl methyl pyrazolone is not considered to be genotoxic. Two *in vitro* genotoxicity tests showed positive results, but all *in vivo* tests were negative.

#### *Mutagenicity*

Phenyl methyl pyrazolone did not induce gene mutations in bacteria. It was also not mutagenic in an *in vitro* gene mutation test with mammalian cells (hprt locus). A mutagenic response was observed in the Mouse Lymphoma assay (tk locus) but only in the presence of S9. In an *in vitro* micronucleus assay no genotoxic effect (structural and/or numerical chromosomal aberrations) was observed. An *in vivo* bone marrow micronucleus assay in mice and an *in vivo* UDS assay in rats were negative. The results of the tests performed indicate that phenyl methyl pyrazolone itself is not mutagenic *in vivo*. To reach a definitive conclusion, the SCCS requested appropriate tests with *m*-aminophenol in combination with hydrogen peroxide have to be provided (SCCS 2006).

#### *Carcinogenicity*

Based on the available data, phenyl methyl pyrazolone is not expected to be carcinogenic.

- In a carcinogenicity study in rats, groups of Fischer 344 (F344) rats (n = 50/sex/dose) were administered phenyl methyl pyrazolone at 0, 2500 or 5000 ppm in the diet for 102 weeks, equivalent to 0, 125 and 250 mg/kg bw/day respectively. There was no dose-relationship or statistical significance in the occurrences of individual tumours between treated and control rats of both sexes.
- In a carcinogenicity study in mice, groups of B6C3F1 mice (n = 50/sex/dose) were administered phenyl methyl pyrazolone at 0, 7500 or 15000 ppm in the diet for 102 weeks. There was no significant association between dosage and mortality, with an 80% or more survival rate in all groups. A number of neoplastic and non-neoplastic lesions were observed in all treated groups, but there was no association or statistical significance between dosage and tumour incidence.

#### *Reproduction and developmental toxicity*

Based on the limited information available, phenyl methyl pyrazolone does not show specific reproductive or developmental toxicity. Developmental effects were only observed secondary to

maternal toxicity. A NOAEL of 200 mg/kg bw/day was determined for both maternal and developmental toxicity incidence.

#### *Public exposure*

The critical health effect for risk characterisation is skin sensitisation. Phenyl methyl pyrazolone is a slight skin irritant at a concentration of 1%.

Phenyl methyl pyrazolone has cosmetic use identified in Australia in hair dye products. No use concentrations of phenyl methyl pyrazolone in these products are available, although it is known to be used overseas at a maximum concentration of 0.25% on the hair. Based on this use, the general public may be exposed to phenyl methyl pyrazolone via dermal contact.

#### ***Pre-meeting public submissions***

Two (2) pre-meeting submission were received, neither of which objected to the proposed scheduling for phenyl methyl pyrazolone.

#### *Main points were:*

- Alignment with the following EU regulations is supported:
  - Phenyl methyl pyrazolone is included in Annex III of the EU Cosmetics Regulation, allowing its use as a hair dye substance in oxidative hair dye products with an in-use concentration (after mixing under oxidative conditions) not exceeding 0.25%.
  - Any warning statements and safety directions should be consistent with those for other scheduled hair dye substances with similar risk profiles, and as much as possible with those required in the EU to allow for harmonisation.
- The implementation date should be 12-24 months to allow for any labelling changes that may be required. These changes could affect products currently in the Australian market with an established history of safe use. There is no evidence that would suggest immediate action is required for the risk management of this substance.
- Phenyl methyl pyrazolone is not entered in the TGA eBS ingredients list, nor is it entered in the TGA Permitted Ingredients List. It is therefore assumed that the scheduling proposal will not impact therapeutic goods. Should any inadvertent impact be revealed, comment will be provided during the public consultation phase of the interim decision.

The public submissions will be made available on the [TGA website](#).

#### ***Summary of ACCS advice to the delegate***

The committee recommended that a new Schedule 6 and Appendix E and F entries for phenyl methyl pyrazolone be created as follows:

##### **Schedule 6 – New Entry**

**PHENYL METHYL PYRAZOLONE except when used in hair dye and eyebrow/eyelash preparations at a concentration of 0.25 per cent or less after mixing for use 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**

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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

### **Appendix F, Part 3 – New Entry**

Warning Statement: 28 ((Over) (repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- Risk: potential skin sensitiser.
- Benefit: use in hair dyes.

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

- Phenyl methyl pyrazolone is used as a hair dye in oxidising hair dyes and possibly other cosmetics.

c) the toxicity of a substance:

- Phenyl methyl pyrazolone is a moderate sensitiser.

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

- The known use of phenyl methyl pyrazolone is as a hair dye, in oxidising hair dyes, with in-use concentration of 0.25% or less. The product is provided in small packages and is intended to be mixed with hydrogen peroxide in 1:1 ratio before use.
- A warning statement on the packaging for potential sensitisation is warranted.

e) the potential for abuse of a substance:

- Nil.

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

- Consumers have extensive experience with the use of hair dye products.
- Harmonises with international regulations.

### **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 Schedule 6 and Appendix E and F entries for phenyl methyl pyrazolone. The proposed Schedule entry is:

#### **Schedule 6 – New Entry**

PHENYL METHYL PYRAZOLONE **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 0.25 per cent or less after mixing for use 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**

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)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

#### **Appendix F, Part 3 – New Entry**

Warning Statement: 28 ((Over) (repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The proposed implementation date is **1 June 2019** to allow for any labelling changes that may be required.

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

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

- Risk: potential skin sensitiser.
- Benefit: use in hair dyes.

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

- Phenyl methyl pyrazolone is used as a hair dye in oxidising hair dyes and possibly other cosmetics.

c) the toxicity of a substance:

- Phenyl methyl pyrazolone is a moderate sensitiser.

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

- The known use of phenyl methyl pyrazolone is as a hair dye, in oxidising hair dyes, with in-use concentration of 0.25% or less. The product is provided in small packages and is intended to be mixed with hydrogen peroxide in 1:1 ratio before use.
- A warning statement on the packaging for potential sensitisation is warranted.

e) the potential for abuse of a substance:

- Nil.

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

- Consumers have extensive experience with the use of hair dye products.
- Harmonises with international regulations.

### 3.7 Dinotefuran

#### ***Referred scheduling proposal***

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the current Schedule 5 entry to exempt preparations containing 10 per cent or less of dinotefuran in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### ***Scheduling application***

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

##### **Schedule 5 – Amend Entry**

DINOTEFURAN **except in preparations containing 10 per cent or less of dinotefuran.**

The applicant's reasons for the request are:

- Toxicity studies of several products containing dinotefuran have confirmed low toxicity consistent with the proposed scheduling.

#### ***Current scheduling status***

Dinotefuran is currently listed in Schedule 5 as follows:

##### **Schedule 5**

DINOTEFURAN.

#### ***Relevant scheduling history***

In July 2015, the ACCS considered a proposal to include dinotefuran in the Poisons Standard. The committee recommended, and the delegate agreed, to include dinotefuran in the Poisons Standard 1 October 2015.

Although other members of the neonicotinoid class are listed in Schedule 6, on [22 July 2015 the delegate made a final decision for dinotefuran](#) to create a new Schedule 5 entry due to its low toxicological profile consistent with the Scheduling Policy Framework (SPF) Schedule 5 criteria. However, evidence of mild/moderate skin/eye irritancy for the formulated product meant that it was inappropriate to provide a schedule exemption for the formulated product considered in the application.

### **Australian regulatory information**

Dinotefuran is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#) and is not an excipient or active in any medicines on the [ARTG](#).

A search of the [Database of Adverse Events Notifications \(DAEN\)](#) database for dinotefuran did not reveal any adverse events or safety issues from 1 January 1971 to 17 May 2017.

Dinotefuran is an APVMA approved active constituent and is contained in one APVMA registered product on the [PubCRIS](#) database.

APVMA [Public Release Summary on the 'Evaluation of the new active Dinotefuran in the Product Starkle 200 SG Insecticide'](#), August 2015

### **International regulations**

#### *The Joint FAO/WHO Meeting on Pesticide Residues (JMPR)*

JMPR have previously evaluated dinotefuran. The report [The Joint FAO/WHO Meeting on Pesticide Residues \(JMPR\) has previously evaluated the toxicology of dinotefuran](#).

#### *European Union*

Dinotefuran was approved for use by the Committee for Medicinal Products for Veterinary Use (CVMP)/the European Medicines Agency's (EMA) in October 2013 as part of the registration a product.

#### *United States of America (USA)*

Dinotefuran was first registered with the USA Environmental Protection Agency in September 2004 by the applicant.

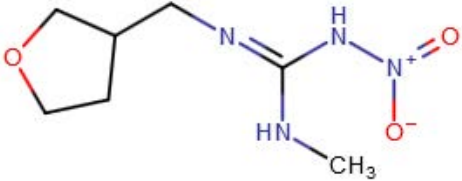
### **Substance summary**

Dinotefuran is a member of the neonicotinoid class of chemicals that act through binding to nicotinic acetylcholine receptors. There are no new data or changes for the active constituent from the acute and repeat-dose toxicology data that was presented at the July 2015 ACCS meeting.

The following information was extracted from the AVPMA human health risk assessment (HHRA) technical report for the toxicology of dinotefuran.

**Table 3.7.1: Chemical information for dinotefuran**

Property	Dinotefuran
CAS name	<i>N</i> -methyl- <i>N'</i> -nitro- <i>N''</i> -[(tetrahydro-3-furanyl)methyl]guanidine

CAS number	165252-70-0
Chemical structure	
Molecular formula	C <sub>7</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>
Molecular weight	202.2 g/mol
IUPAC and/or common and/or other names	1-Methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine (IUPAC); 2-Methyl-1-nitro-3-(oxolan-3-ylmethyl)guanidine; 1-Methyl-2-nitro-3-((tetrahydrofuran-3-yl)methyl)guanidine; <i>N</i> ( <i>RS</i> )-1-methyl-2-nitro-3-[(tetrahydro-3-furanyl) methyl] guanidine; MTI-446.

**Table 3.7.2: Acute toxicity end-points for dinotefuran**

Toxicity	Species	Dinotefuran	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	Rat	2450	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	Rat	>2000 (no deaths)	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	Rat	>4090 (no deaths)	Schedule 5
Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Moderate	Schedule 5
Skin sensitisation (GPMT)	Guinea pig	Not sensitising	N/A

#### Summary of products

- Dust Insecticide (DU, dust), 2.5 g/kg dinotefuran;
- Pressurised Fly Bait (AE), 10 g/kg dinotefuran;
- Gel Cockroach Bait (BA, gel bait), 5 g/kg dinotefuran;

- Pressurised Insecticide (PI or AE, aerosol), 5 g/kg dinotefuran;
- WSG Insecticide (WG, water-soluble granules), 400 g/kg dinotefuran.<sup>58</sup>

The submitted acute toxicity data supports a cut-off for dinotefuran from Schedule 5 at 10 per cent. Acute toxicity is summarised below.

**Table 3.7.3: Acute toxicity end-points for dinotefuran product formulations**

Toxicity <sup>59</sup>	Dust (DU)	Pressurised fly bait (AE)	Pressurised insecticide PI (AE)	Gel Bait (BA)	Water-soluble granules (WG)
Dinotefuran Concentration (g/kg)	2.5	10	5	5	400
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	> 5000	> 5000	> 5000	> 5000	> 5000
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	> 5000	> 5000	> 5000	> 5000	> 5000
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	> 2080	> 5090	> 2050	> 2070	> 5090
Skin irritation	Non-irritant	Non-irritant	Slight	Non-irritant	Non-irritant
Eye irritation	Moderate – due to abrasive ground rock in formulation, not due to active	Very slight	Slight	Slight	Moderate
Skin sensitisation (Buehler)	Not sensitising	Not sensitising	Not sensitising	Not sensitising	Not sensitising
SPF (2015) Classification	Schedule 5/6	N/A-Schedule 5	Schedule 5/6	Schedule 5/6	Schedule 5

The proposed products all have low acute oral, dermal and inhalational toxicity, and none were skin sensitisers. The toxicity endpoints relevant to scheduling are skin and eye irritation. More details from these relevant acute toxicity studies on the products are summarised below in Table 3.

**Table 3.7.4: Details for dinotefuran skin and eye irritation toxicity studies**

Toxicity <sup>60</sup>	Dust (DU)	Pressurised fly bait (AE)	Pressurised insecticide PI	Gel Bait (BA)	Water-soluble granules (WG)
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<sup>58</sup> The Human Health Risk Assessment Technical Report by the APVMA contains consideration of a water-soluble granule product formulation containing 40% w/v dinotefuran – but is not subject to the current re-scheduling request

<sup>59</sup> Standard species used (rat, rabbit, guinea pig, as appropriate)

<sup>60</sup> Standard species used (rat, rabbit, guinea pig, as appropriate)

			(AE)		
Dinotefuran Conc (g/kg)	2.5	10	5	5	400
Skin irritation NZ White rabbits, n=3 Results:	0.5 g (1.25 g of the 40% w/w test mixture). Very faint erythema (score of 0.3) at 1 h post-application; Fully resolved by 24 h.	0.5 g. No observed erythema or oedema	0.5 g. Erythema (score of 1) in all rabbits at 1 h post-application, remaining in 2/3 animals at 24 hours, and fully resolving by 48 h.	0.5 mL. Very slight erythema (score of 1) mean in 3/3 rabbits at 1 h post-application. Full recovery at 24 h.	40% solution. No erythema or oedema was observed.
Conclusion	Non-irritant	Non-irritant	Slight irritant	Non-irritant	Non-irritant
Eye irritation NZ White rabbits, n=3 Results:	0.03 g. Conjunctivitis and iritis in all animals within 1 h post-instillation; resolved by Day 7. One animal exhibited corneal opacity by 24 h, resolved by Day 4 was observed in the experimental period.	A 'burst' (0.3-0.5 g) to the right eye from a distance of approximately 10 cm. Very slight (scores of 1/3) conjunctivae redness, and discharge in 2/3 eyes each at 1 h, fully resolved by 24 h.	0.1 mL. Conjunctivitis in all animals at 1 h; recovery by 48 h. No corneal opacity or iritis were observed in the experimental period.	0.1 mL. Conjunctivitis observed in all treated eyes within 1 h post-instillation, remaining in 1/3 eyes at 24 h, and fully resolving at 48 h.	0.07 g (0.1 mL). Conjunctivitis and corneal opacity observed in all animals at 24 h, partially resolving at 48 h, and fully resolving by 72 h.
Conclusion	Moderate irritant (due to ground rock in formulation, not due to active ingredient)	Very slight irritant	Slight irritant	Slight irritant	Moderate irritant

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACCS advice to the delegate***

The committee recommended that the current Schedule 5 entry for dinotefuran be amended as follows:

#### **Schedule 5 – Amend Entry**

DINOTEFURAN **except in preparations containing 1 per cent or less of dinotefuran.**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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 recommendation comprised the following:

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

- Risks: dinotefuran has a potential for slight-moderate reversible eye irritancy.
- Benefit: dinotefuran is a low-risk insecticide for both agricultural and commercial use, with possible domestic use.

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

- Dinotefuran is a neonicotinoid, a relatively newer class of insecticide.

c) *the toxicity of a substance:*

- Ready to use products containing dinotefuran are both slight eye irritants and skin irritants.

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

- Packaging and labelling consistent with APVMA requirements.

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

- Nil.

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

- New data provided supports the recommended cut-off. This was not available in 2015 when dinotefuran was first entered into the Poisons Standard.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

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

### ***Delegate's interim decision***

The delegate's interim decision is to amend the current Schedule 5 entry of dinotefuran. The proposed Schedule entry is:

#### **Schedule 5 – Amend Entry**

DINOTEFURAN **except** in preparations containing 1 per cent or less of dinotefuran.

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.



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

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

- Risks: dinotefuran has a potential for slight-moderate reversible eye irritancy.
- Benefit: dinotefuran is a low-risk insecticide for both agricultural and commercial use, with possible domestic use.

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

- Dinotefuran is a neonicotinoid, a relatively newer class of insecticide.

c) *the toxicity of a substance:*

- Ready to use products containing dinotefuran are both slight eye irritants and skin irritants.

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

- Packaging and labelling consistent with APVMA requirements.

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

- Nil.

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

- New data provided supports the recommended cut-off. This was not available in 2015 when dinotefuran was first entered into the Poisons Standard.

### 3.8 Afidopyropen

#### ***Referred scheduling proposal***

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to consider afidopyropen for scheduling in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

#### ***Scheduling application***

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

#### **Appendix B – New Entry**

#### **AFIDOPYROPEN**

The applicant's reasons for the request are:

- The available toxicological data for afidopyropen is considered to be sufficient for the purposes of recommending a scheduling decision.
- The toxicity hazard profile for acute exposure to afidopyropen does not warrant a schedule.

- Afidopyropen's mode of action may be similar to another insecticide, pymetrozine, which is in Schedule 5 on the basis of moderate acute eye irritation.

### ***Current scheduling status***

Afidopyropen is not currently scheduled.

The applicant states that the mode of action of Afidopyropen may be similar to another insecticide, pymetrozine (see [Substance summary](#) below), which is in Schedule 5 of the [Poisons Standard](#) as follows:

#### **Schedule 5**

PYMETROZINE.

### ***Relevant scheduling history***

Afidopyropen is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available

#### *Scheduling history of pymetrozine*

In February 1997, the National Drugs and Poisons Schedule Committee (NDPSC) considered an application to create a new Schedule 5 entry for pymetrozine. The committee considered toxicological data and considered that Schedule 5 was appropriate for pymetrozine on the basis of moderate eye irritation in the rabbit.

### ***Australian regulatory information***

Afidopyropen is not currently registered with the APVMA as an active constituent or product.

Afidopyropen is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2017](#), and is not an excipient or active in any medicines on the [ARTG](#).

### ***International regulations***

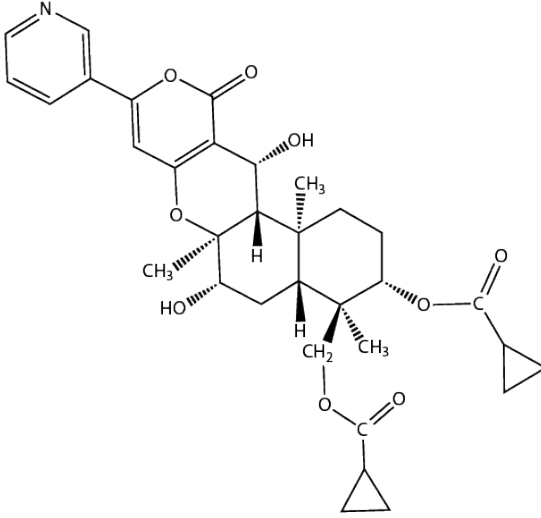
- Applications for the approval of afidopyropen and its products have also been submitted in the United States of America, Canada and Mexico
- Afidopyropen is not on the Environmental Protection Agency approved pesticide list.
- Afidopyropen is being studied in Canada under the minor use pesticide program.
- From the Codex Committee on Pesticide Residues: Afidopyropen is on the 2019 list of new compound evaluations for the Joint Food and Agriculture Organization of the United Nations/World Health Organisation Food Standards Programme for pesticide residues.

### ***Substance summary***

Afidopyropen (ISO approved name) is the first member of a new chemical class of insecticides that has not been previously considered by the Chemicals Scheduling Delegate or Advisory Committee on Chemicals Scheduling (ACCS).

A recent published report (May, 2017) suggests that its mode of action may be similar another insecticide pymetrozine, in that it overstimulates and eventually silences vanilloid-type transient receptor potential (TRPV) channels which are expressed exclusively in insect chordotonal stretch receptor neurons.<sup>61</sup> The consequence of this binding is to inhibit plant-sucking insects' ability to feed, resulting in starvation and eventually death. Afidopyropen and pymetrozine have overlapping binding sites, with afidopyropen having higher affinity than pymetrozine. Pymetrozine is in Schedule 5 on the basis of moderate acute eye irritation.

**Table 3.8.1: Chemical information for Afidopyropen**

Property	Afidopyropen
CAS number	915972-17-7
Chemical structure	<p>C<sub>33</sub>H<sub>39</sub>NO<sub>9</sub></p> 
IUPAC, CAS and/or common and/or other names	<p>[(3<i>S</i>,4<i>R</i>,4<i>aR</i>,6<i>S</i>,6<i>aS</i>,12<i>R</i>,12<i>aS</i>,12<i>bS</i>)-3-(cyclopropylcarbonyloxy)-1,2,3,4,4<i>a</i>,5,6,6<i>a</i>,12<i>a</i>,12<i>b</i>-decahydro-6,12-dihydroxy-4,6<i>a</i>,12<i>b</i>-trimethyl-11-oxo-9-(3-pyridyl)-11<i>H</i>,12<i>H</i>-benzo[<i>f</i>]pyrano[4,3-<i>b</i>]chromen-4-yl]methyl cyclopropanecarboxylate (IUPAC);</p> <p>[(3<i>S</i>,4<i>R</i>,4<i>aR</i>,6<i>S</i>,6<i>aS</i>,12<i>R</i>,12<i>aS</i>,12<i>bS</i>)-3-[(cyclopropylcarbonyl)oxy]-1,3,4,4<i>a</i>,5,6,6<i>a</i>,12,12<i>a</i>,12<i>b</i>-decahydro-6,12-dihydroxy-4,6<i>a</i>,12<i>b</i>-trimethyl-11-oxo-9-(3-pyridinyl)-2<i>H</i>,11<i>H</i>-naphtho[2,1-<i>b</i>]pyrano[3,4-<i>e</i>]pyran-4-yl]methyl cyclopropanecarboxylate (CAS)</p>

The following information was extracted from APVMA assessment report [Interim Human Health Technical Report – afidopyropen – Versys Insecticide (BAS 440 001)].

**Table 3.8.2: Acute toxicity end-points for afidopyropen**

<sup>61</sup> Kandasamy R *et al.*, (2017) Afidopyropen: New and potent modulator of insect transient receptor potential channels. *Insect Biochem Mol Biol* **84**: 32-39.

Toxicity	Species	Afidopyropen	SPF (2015) Classification
Acute oral toxicity LD <sub>50</sub> (mg/kg bw)	rat	>2000 (no deaths)	Schedule 5
Acute dermal toxicity LD <sub>50</sub> (mg/kg bw)	rat	>2000 (no deaths)	Schedule 5
Acute inhalational toxicity LC <sub>50</sub> (mg/m <sup>3</sup> /4h)	rat	>5480 (no deaths)	Schedule 5
Skin irritation	rabbit	Non-irritating	N/A
Eye irritation	rabbit	Slight (with ground powder)	Schedule 5
Skin sensitisation (GPMT)	Guinea pig	Non-sensitising	N/A

#### *Acute toxicity*

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

#### *Skin irritation*

Based on available data from an OECD Guideline-compliant study in rabbits, afidopyropen is not a skin irritant:

- Three female rabbits received a single (semi-occlusive) topical application of 0.5 g afidopyropen moistened with 0.5 mL de-ionised water for 4 h. Observation for skin irritation was performed at 1, 24, 48 and 72 h after patch removal. Observations for signs of toxicity were made once daily. There were no clinical signs or dermal erythema, eschar or oedema.

#### *Eye irritation*

Based on available data, afidopyropen in a fine powder is a slight eye irritant:

- Six female rabbits were administered 0.1 g afidopyropen (powder) by ocular instillation. The eyes of three rabbits were irrigated with lukewarm water after 30 seconds. Observation for ocular irritation was performed at 1, 24, 48 and 72 h after instillation. Observations for signs of toxicity were made once daily. All rabbits survived until termination and displayed no clinical signs other than eye irritation. No corneal opacity or iritis occurred, but grade 1 (hyperaemia) conjunctival redness was present in two of three washed and two of three unwashed eyes at the 1-hour observation (see following table). Concomitantly, oedema grade 1 (above normal) or grade 2 (swelling with eyelids everted) was noted in two of three unwashed eyes, and all three unwashed eyes displayed discharge grade 1 (above normal), grade 2 (moistened eyelids and adjacent area) or grade 3 (moistened eyelids and wide surrounding area). Calculated by the method of Kay and Calandra, in unwashed eyes (animals 1 – 3), the highest mean total irritation score was 7.3 at 1 h after application. All signs of conjunctival irritation resolved within 24 h, and the observation period was ended at 72 h in the absence of any further findings. Under the study conditions described, afidopyropen was a slight eye irritant.

### *Sensitisation*

Based on available data using the guinea pig maximisation test method according to OECD guidelines, afidopyropen is not a skin sensitiser.

### *Repeat-dose toxicity*

Repeat-dose toxicity studies indicate:

- 28 and 90-day oral toxicity in mice – increased circulating bilirubin levels
- 28-day oral toxicity in rats suggested that the liver, female reproductive system, renal system and haematopoietic system are possible target organs for the test compound in rats by dietary administration
- 90-day oral rat - based on haematological abnormalities, increased urinary excretion of urobilinogen and protein, elevated blood potassium and BUN levels and ALT and AST activity, hepatic enlargement, and histopathological abnormalities within the liver and heart at and above a dietary concentration of 1000 ppm, the NOAEL was 300 ppm, equal to 18.3 mg/kg bw/d
- 90-day oral (gelatin capsules) dog - the NOAEL was 15 mg/kg bw/d, based on vomiting, reduced bodyweight gain and toxicity to the liver at and above the next highest dose of 30 mg/kg bw/d
- 1-yr oral (gelatin capsules) dog - based on vacuolation within brain tissues, biochemical and histological evidence of liver injury, and histological abnormalities in the intestine and gall bladder at 20 mg/kg bw/d and above, the NOAEL was 8 mg/kg bw/d. The depression in bodyweight and bodyweight gain in males at 8 mg/kg bw/d is discounted because bodyweight gain was increased in females treated at this dose

### *Genotoxicity*

Afidopyropen gave negative results in an adequate range of assays for genotoxicity *in vitro* and *in vivo*.

### *Carcinogenicity*

Having regard to the submitted experimental findings (see assessment report) on afidopyropen and available body of evidence from experimental and clinical studies with bromocriptine and other dopamine agonists, the reviewing toxicologist has concluded that afidopyropen should be regulated as a non-genotoxic, threshold dose, reproductive system carcinogen in female rats, which is of low relevance and risk to humans under the anticipated magnitude and conditions of exposure.

### *Reproduction and developmental toxicity*

The NOAEL in rats for reproductive toxicity was 1500 ppm (equal to 122 mg/kg bw/d in dams) due to impaired implantation at and above the maternal dose of 3000 ppm. The NOAEL for parental toxicity was 150 ppm (equal to 9.6 mg/kg bw/d in dams) based on depressed seminal vesicle weight, maternal food consumption and gestational bodyweight gain, and increased maternal liver weight at 1500 ppm and above. The NOAEL for offspring toxicity was 150 ppm (equal to 9.6 mg/kg bw/d) based on increased post-natal mortality, depressed bodyweight and decreased spleen weight in pups at and above the maternal dose of 1500 ppm.

In rats, a concentration of 1500 ppm (equal to 122 mg/kg bw/d in dams) afidopyropen in the parental diet did not cause developmental malformations in pups exposed *in utero*. In another rat study, under the study conditions, afidopyropen did not cause foetal malformations at up to 100 mg/kg bw/d, the highest dose administered. In rabbits, the NOAEL for effects on foetal survival, growth and

development was 32 mg/kg bw/d, the highest administered dose. Under the study conditions, afidopyrofen did not cause developmental malformations in rabbits.

### ***Pre-meeting public submissions***

No submissions were received.

### ***Summary of ACCS advice to the delegate***

The committee recommended that afidopyrofen be included in Schedule 5 as follows:

#### **Schedule 5 – New Entry**

#### **AFIDOPYROPEN.**

The committee also recommended an implementation date of **1 June 2018** as this is the earliest practicable implementation date.

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

The reasons for the recommendation comprised the following:

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

- Risks: acute toxicity appears to be low. However, in repeat dose studies the low dose effect was seen in offspring as well as the liver.
- Benefit: the benefit is to horticultural industry, where this chemical presents as another insecticide option.

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

- Nil.

c) *the toxicity of a substance:*

- There are reservations regarding repeat dose studies and in offspring.

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

- Nil.

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

- Nil.

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

- This is a new chemical class that has similar mechanism of action to existing Schedule 5 entries.

### ***Delegate's considerations***

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice

- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information

### ***Delegate's interim decision***

The delegate notes the committee's advice. However, the delegate's interim decision is to create a new Appendix B entry for afidopyropen in the Poisons Standard. The proposed Schedule entry is:

#### **Appendix B – New Entry**

##### AFIDOPYROPEN

Reasons for Entry: b (Use pattern restricts hazard)

Areas of Use: 1.2 (Insecticide)

The proposed implementation date is **1 June 2018**. This is the earliest practicable implementation date.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of the substance; (c) the toxicity of the substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

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

- Risks: the acute toxicity profile is low and of no relevance to humans.
- Benefit: the benefit is to horticultural industry, where afidopyropen presents as another insecticide option.

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

- Nil.

c) *the toxicity of a substance:*

- The low acute toxicity profile does not warrant inclusion in a schedule.
- The delegate is of the opinion that the low dose effects seen in repeat dose studies are unlikely to be achieved in humans and are therefore of no relevance to humans, particularly when the product is used in accordance with directions.

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

- Nil.

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

- Nil.

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

- Although this is a new chemical class that has similar mechanism of action to existing Schedule 5 entries, there is insufficient data to warrant inclusion in Schedule 5.
- Inclusion in Appendix B will not prevent reconsideration of the scheduling of afidopyropen where adverse information becomes available about its Appendix B entry