Australian Government

Department of Health
Therapeutic Goods Administration

Final decisions amending, or not amending, the current Poisons Standard, November 2018

29 November 2018

Scheduling amendments referred to expert advisory committee

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

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

Pursuant to regulation 42ZCZK, the Secretary must invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice. Such a notice relating to the final decisions referred to herein was made available on the TGA website on 12 April 2018 and the opportunity to make submissions closed on 10 May 2018. Public submissions received on or before this closing date were published on the TGA website at Public submissions on scheduling matters referred to the ACMS #24 and Joint ACMS-ACCS #19 meetings held in June 2018 in accordance with subregulation 42ZCZL(3).

Under regulation 42ZCZN of the Regulations, the Secretary, after considering the advice or recommendation of the expert advisory committee, must (subject to regulation 42ZCZO) make an interim decision in relation to the proposed amendment.

Under regulation 42ZCZP of the Regulations, the Secretary must, among other things, publish as soon as practicable (in a manner the Secretary considers appropriate) a notice setting out the interim decision and the reasons for making the interim decision and the proposed date of effect of the proposed amendment (if any).

Also in accordance with regulation 42ZCZP of the Regulations, the Secretary must invite interested persons to make further submissions to the Secretary in relation to the interim decisions by a date mentioned in the notice as the closing date, allowing at least 10 business days after publication of the notice. Such a notice relating to the interim decisions of substances initially referred to the June 2018 meetings of the Advisory Committee on Medicines Scheduling (ACMS #24) and the Joint Advisory Committee on Medicines and Chemicals Scheduling (ACMS #19) was made available on the TGA website on 10 September 2018 and closed on 11 October 2018 (Publication of interim decisions amending, or not amending, the current Poisons Standard, September 2018). Public submissions received on or before this closing date will be

published on the TGA website (Public submissions on scheduling matters) in accordance with regulation 42ZCZQ.

Under regulation 42ZCZR of the Regulations, the Secretary may make a final decision by confirming, varying or setting aside the interim decision, but only after considering all relevant submissions and any advice received in response to a request under paragraph 42ZCZQ(2)(a).

In deciding whether to amend the current Poisons Standard, the Secretary must take into account the matters mentioned in subsection 52E (1) of the Act. These matters include for example, the risks and benefits of the use of a substance, and the potential for abuse of a substance. The Secretary must also comply with (among others) any guidelines of the Australian Health Ministers' Advisory Council referred to the Secretary for the purposes of section 52E of the Act including those set out in the *Scheduling Policy Framework for Medicines and Chemicals*.

Scheduling amendments not referred to expert advisory committee

Subdivision 3D.3 of the Regulations sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the Act to amend the current Poisons Standard and decides not to refer the proposed amendment to an expert advisory committee.

Publication of decisions pursuant to regulations 42ZCZS and 42ZCZX of the Therapeutic Goods Regulations 1990

In accordance with regulations 42ZCZS and 42ZCZX, this notice gives effect to the Secretary's obligation to publish the final decisions, the reasons for those decisions and the date of effect of decisions made pursuant to regulations 42ZCZR, 42ZCZU or 42ZCZW of the Regulations.

The final decisions to which this notice relates include decisions made with respect to:

- scheduling proposals initially referred to the June 2018 meeting of the Advisory Committee on Medicines Scheduling (ACMS #24);
- scheduling proposals initially referred to the June 2018 meeting of the Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS #19); and
- scheduling proposals on agricultural and veterinary chemicals which were not referred to an expert advisory committee.

Privacy and your personal information

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

The TGA is part of the Department of Health. For general privacy information, a link to the Department's privacy policy, and for contact information if you have a query or concerns about a privacy matter, go to Privacy.

The TGA may receive submissions from the public on a proposed amendment to the Poisons Standard where there has been an invitation to the public for submissions on the proposal in

accordance with the *Therapeutic Goods Regulations 1990*. These submissions may contain personal information of the individual making the submissions and others.

The TGA collects this information as part of its regulatory functions and may use the information to contact the individual who made the submissions if the TGA has any queries.

As set out above, the TGA is required to publish these submissions unless they contain confidential information.

If you request for your submission to be published in full, including your name and any other information about you, then the TGA will publish your personal information on its website. However, if at any point in time, you change your mind and wish for your personal information to be redacted then please contact the Scheduling Secretariat at medicines.scheduling@health.gov.au so that the public submissions can be updated accordingly.

Please note that the TGA cannot guarantee that updating the submissions on the TGA website will result in the removal of your personal information from the internet.

Please note that the TGA will not publish personal information about you/others without your/their consent unless authorised or required by law.

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Part A - Amendments to the Poisons Standard referred to expert advisory committee

1. Advisory Committee on Medicines Scheduling (ACMS #24)

1.1. Sildenafil

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is not to amend the current Poisons Standard in relation to sildenafil.

Reasons:

The delegate has confirmed that the reasons for the final decision align with the reasons for the interim decision. Additional reasons for the final decision are the following:

- The applicant claims that most patients for whom sexual activity does not represent a cardiac risk can initiate or resume sexual activity and begin ED treatment without further testing or evaluation. However, CVD cannot be diagnosed by a pharmacist, and the list of diagnosis tools (including ECG and other cardiac testing) recommended by the Princeton III Consensus Recommendations for the Management of ED and CVD are not possible in a pharmacy setting[1].
- Although there were proposed education and checklist material included in the application it was not felt that these would mitigate the risks of down scheduling. These did not appear to address:
  - Requirements for pharmacists to have written documentation of their consultation, outlining the clinical assessment they undertook and whether they supplied medication or referred.
  - Well-developed clinical referral pathways for pharmacists that must be adhered to.
  - The pharmacy checklist states "The following has been created as a useful aide-memoire to help determine whether your patient is suitable for [redacted], or whether he should be seen by a doctor for further advice. You should use your professional judgement to decide when and how to use this Checklist." This means that it is not seen as having to be used by the pharmacist.
  - The checklist also states: "You should consider possible causes of erectile dysfunction, such as undiagnosed depression, anxiety, excessive alcohol use and taking certain medicines." The ability of a pharmacist to diagnose some of these conditions such as undiagnosed depression and anxiety is questioned.
  - Based on the information provided, the additional controls proposed for Schedule 3 sildenafil supply were not considered to be sufficient Appendix M criteria for ED and sildenafil treatment given that ED is a symptom of other conditions which require medical practitioner diagnosis, monitoring and treatment.

[1] Nehra et al. (2012) 'The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease', *Mayo Clin Proc*, 87(8), 766-778

Public submissions on the interim decision

Two (2) public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. Both submissions opposed the interim decision.

The main points provided in opposition of the amendment were:

- Sildenafil meets the S3 criteria rather than those of S4 because erectile dysfunction is a self-recognised/self-diagnosed condition.
- During the Scheduling Stakeholder Forum held 6 March 2018 TGA used sildenafil as a case study to facilitate discussions on Appendix M. It was surprising, then, that the Record of Reason included the statement that 'Appendix M is not appropriate for ED and sildenafil treatment given that ED is a symptom of other conditions which require medical practitioner diagnosis, monitoring and treatment.' Appendix M is appropriate for ED and sildenafil. The submission claims that additional controls for Schedule 3 sildenafil that could be incorporated in Appendix M would ensure safe and appropriate supply of the product.
- The record of reasons should revise the statement saying no education or checklist material was provided in the submission, as this is not accurate.
- Request: the statement regarding down scheduling being not an appropriate mechanism to address counterfeit sildenafil be removed, as this was not claimed in the application.
- Data provided was not taken into account that men are being prescribed in most cases a PDE5 inhibitor in the current primary care setting without additional diagnostic testing of the underlying cause
- The Delegate cited the diagnosis tools for risk factors of ED in the Princeton III Consensus but failed to mention its recommendation that most patients for whom sexual activity does not represent a cardiac risk can initiate or resume sexual activity and begin ED treatment without further testing or evaluation.
- It is unclear why the safety profile of sildenafil is still considered a concern given robust evidence was provided.
- The Delegate noted that the limited pack size does not address risk to consumers; however, the proposed labelling included the appropriate warnings that would facilitate correct and safe use of the medicine, rather than simply being limited to pack size.
- Too little emphasis on the potential benefits of re-scheduling were placed by the ACMS and the Delegate and they dismissed the recent and relevant decisions made by comparable overseas regulatory authorities on the public health benefit of increased access.

Interim decision

The interim decision for sildenafil was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACMS, September 2018 – 1.1 Sildenafil.

Scheduling proposal

The pre-meeting scheduling proposal for sildenafil was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

1.2. Budesonide

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to budesonide as follows:

Schedule 2 – Amend Entry

BUDESONIDE in aqueous nasal sprays delivering ~~50~~64 micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms ~~and when packed in a primary pack containing 200 actuations or less~~, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Schedule 4 – (No change)

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

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BUDESONIDE

Schedule 4
Schedule 2

Implementation date: 1 February 2019

Reasons:

As no new evidence has been received to alter the interim decision for budesonide, the delegate has confirmed that the final decision and reasons for the final decision are identical to the interim decision.

Public submissions on the interim decision

Two (2) public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. Both submissions were in support of the interim decision.

The main point provided in support of the amendment was:

- Agree with the delegate's interim decision that the S2 entry for budesonide be amended to increase the dose per actuation from 50 to 64 micrograms and remove the limit of 200 actuations, as budesonide has an excellent safety profile.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACMS, September 2018 – 1.2 Budesonide.

Scheduling proposal

The pre-meeting scheduling proposal for budesonide was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

1.3. Alkyl nitrites

Prior to making a final decision on possible amendments to the Poisons Standard for alkyl nitrites and lubricants, the delegate has requested that further public consultation be undertaken. Information about this consultation was published on the TGA website on 22 November 2018.

1.4. Codeine

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is not to amend the current Poisons Standard in relation to codeine.

Reasons:

As no new evidence has been received to alter the interim decision for codeine, the delegate has confirmed that the final decision and reasons for the final decision are identical to the interim decision.

Public submissions on the interim decision

No public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCKP of the Regulations.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACMS, September 2018 – 1.4 Codeine.

Scheduling proposal

The pre-meeting scheduling proposal for codeine was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

1.5. Cannabidiol and tetrahydrocannabinoids

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is not to amend the current Poisons Standard in relation to cannabidiol and tetrahydrocannabinoids.

Reasons:

The delegate has confirmed that the reasons for the final decision align with the reasons for the interim decision. Additional reasons for the final decision are the following:

- Cannabinoids may have benefits in a range of indications. While cannabidiol is not psychoactive, THC and selected other cannabinoids are, and this underlies the differing scheduling status of cannabidiol (Schedule 4) and tetrahydrocannabinols (Schedule 8).
- The Poisons Standard is a record of decisions on the scheduling of substances, not products. No adequate evidence has been provided to show that THC concentrations up to 1% are safe and have no psychotropic effects. No additional information was provided on the risks and benefits of tetrahydrocannabinol (THC) or other non-cannabidiol cannabinoids to justify their down-scheduling.
- THC is considered to be an 'impurity' of cannabidiol for the purposes of the cannabidiol schedule entry, and the amounts of this impurity must be specified in relation to amount of the active substance, in accordance with TGA-adopted ICH guidelines.[2]

Public submissions on the interim decision

One (1) public submission was received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. The submission was in support of the interim decision.

The main points provided in support of the interim decision were:

- No changes should be made as the safety of a product is better determined by the total amount of active pharmaceutical ingredient consumed rather than the concentration across the final dose form.
- 1% THC across the whole product may allow some companies to circumvent the system.

The main points provided against:

One (1) public submission was received after the second closing date, and was opposed to the interim decision. The submission raised three additional points on the psychotropic threshold of THC in oral formulations.

[2] ICH Topic Q3A (R2) October 2006. Impurities in new Drug Substances; CPMP/ICH/2737/99; ICH Topic Q3B (R2) June 2006. Impurities in new drug products. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf

- A study was provided[3] containing details of the limits required for THC psychotropic effects in individuals. From this study it was claimed that:
  - Oral formulations only have a bioavailability of 10-20%; and
  - The minimum amount of THC for psychotropic effects per individual is 10-20mg. This is well above the recommended maximum dose of 2 mL (2 mg THC) three times per day.
- The two applicants who 'opposed' the proposal appeared to not understand it as they made no mention of THC. Their comments were only about CBD and appeared to be neutral.
- The current (proposed) wording is flawed and should be changed as it does not give a true indication of THC content within cannabinoid products. Having a relative percentage as opposed to an absolute one is problematic as illustrated by the example below where a product with 10 times the amount of THC and potentially psychotropic is Schedule 4.
  - Product A ([redacted]) 1 mg THC 20 mg CBD per ml = 4.7% of the total cannabinoid content (only 0.1% w/v) -Schedule 8 in the current Poisons Standard.
  - Product B, 1 mg THC 50 mg CBD per mL = 1.9% of the total cannabinoid content (0.1% w/v) -Schedule 4 in the current Poisons Standard.
  - Product C, 10 mg THC 500 mg CBD per mL = 1.9% of the total cannabinoid content (1% w/v) -Schedule 4 in the current Poisons Standard.
- The submission claims that the above three points are clearly in line with the ACMS advice that CBD is indeed the dominant ingredient and THC is not psychoactive in this formulation.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACMS, September 2018 – 1.5 Cannabidiol and tetrahydrocannabinols (THCs).

Scheduling proposal

The pre-meeting scheduling proposal for cannabidiol and tetrahydrocannabinoids was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

[3] Grotenhermen F. (2001). Harm reduction associated with inhalation and oral administration of cannabis and THC. *Journal of Cannabis Therapeutics* **1(3/4)**:133-152.

1.6. Ibuprofen combined with paracetamol

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is not to amend the Poisons Standard in relation to ibuprofen combined with paracetamol.

Reasons:

The delegate notes the public submission opposing the interim decision. The reasons for the final decision align with the reasons for the interim decision. Additional reasons for the final decision are the following:

- Increasing pack size from 10 days' supply (30 tablets) to 17 days' supply (50 tablets) may encourage self-treatment of chronic pain. Treatment of chronic pain is outside the approved acute short term pain indication (e.g. migraine headache, tension headache) for S3 paracetamol ibuprofen combinations. This could result in the consumer delaying seeking further advice from a health practitioner. This may result in delayed diagnosis of a chronic condition, a longer recovery period, and potential long term morbidity, which will have an increased impact on the healthcare system. The availability of larger quantities of any analgesic increases the likelihood of misadventure. Consumers should only have access to clinically appropriate quantities.

On balance, I consider that the perceived benefits of larger pack sizes from a convenience perspective are outweighed by the risks.

Public submissions on the interim decision

One (1) public submission was received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. The submission was in opposition of the interim decision.

The main point provided in opposition of the amendment was:

- The Schedule 3 and Schedule 4 entries should have been revised as proposed by the applicant. Such revisions would have better reflected the current scheduling principles and would have been a move towards closer alignment with the New Zealand scheduling of the combination.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACMS, September 2018 – 1.6 Paracetamol combined with ibuprofen.

Scheduling proposal

The pre-meeting scheduling proposal for ibuprofen combined with paracetamol was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS/ACMS #19)

2.1. 2-Butoxyethanol

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to 2-Butoxyethanol as follows:

Schedule 6

2-BUTOXYETHANOL and its ACETATES **except**:

a) in plant growth regulator preparations containing 20 percent or less of such substances; or

b) in other preparations containing 10 percent or less of such substances.

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2-BUTOXYETHANOL

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

Implementation date: 1 February 2019

Reasons:

The delegate has confirmed that the reasons for the final decision align with those for the interim decision, and are as follows:

- 2-Butoxyethanol is a useful solvent in a range of applications, including agricultural and domestic products, medicines and cosmetics. It has low to moderate acute toxicity via oral, dermal and inhalation routes, but can produce severe skin and eye irritancy. A Schedule 6 cut-off concentration of 20% is considered to be too high for general consumer use in domestic products.
- 2-Butoxyethanol is used as a solvent in a range of industrial, trade and domestic cleaning applications, including surface cleaners, floor strippers, paints, laundry detergents, rust removers, and oven and carpet cleaners. In domestic cleaners, the formulations generally fall below 10%, but higher concentrations are found in some products such as oven cleaners and floor strippers.
- 2-Butoxyethanol is readily absorbed via all routes of exposure (inhalation, dermal, ingestion) with low to moderate acute toxicity via oral, dermal and inhalation routes. Its respiratory, skin and eye irritancy are consistent with Schedule 6 factors of the SPF.
- The most sensitive toxicological end point is the destruction of red blood cells (haemolysis). Rats[4] are more susceptible to haemolytic effects than humans, but they develop tolerance

[4] Concise International Chemical Assessment Document 10 - 2-Butoxyethanol, World Health Organization, Geneva 1998

and show reduced haemolytic effects over time, or on future exposure. Additional toxicities include neurotoxicity (loss of coordination, sluggishness and narcosis) and nephrotoxicity. *In-vitro* studies show no mutagenicity or genotoxicity.

- The toxicity of 2-Butoxyethanol is mitigated when formulated as a plant grown regulator, allowing a higher percentage cut off than in products for domestic use. Although the inhalation and skin and eye irritation data of a 20% 2-Butoxyethanol preparation aligns with the Schedule 5 SPF factors, I am satisfied that the mandatory GHS labelling of plant growth regulator preparations as regulated by the APVMA is sufficient to exempt 2-Butoxyethanol from Schedule 6 in such preparations.

Public submissions on the interim decision

No public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS, September 2018 – 2.1 2-Butoxyethanol.

Scheduling proposal

The pre-meeting scheduling proposal for codeine was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

2.2. Dimethyl sulfoxide (DMSO)

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to dimethyl sulfoxide as follows:

Schedule 6 – Amend Entry

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

a) when not for therapeutic use; or

b) in cosmetic preparations; or

c) for the treatment of animals:

i) when combined with no other therapeutic substance(s);

ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or

iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide; or

d) in other preparations **except** when containing 10 per cent or less of dimethyl sulfoxide.

Schedule 4 – Amend Entry

DIMETHYL SULFOXIDE (excluding dimethyl sulfone) in preparations for therapeutic use **except**:

a) when included in Schedule 6; or

b) in in vitro test kits; or

c) when used as a flavour component in compliance with the current Therapeutic Goods (Permissible Ingredients) Determination for listed medicines.

Appendix E, Part 2

DIMETHYL SULFOXIDE

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), G3 (If swallowed, do NOT induce vomiting), E1 (If in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water)

Appendix F, Part 3

DIMETHYL SULFOXIDE	Warning Statement	Safety Direction
a) when not packed and labelled for therapeutic	27 (Not for therapeutic use)	1 (Avoid contact with eyes), 4 (Avoid contact with skin), 5 (Wear

use.		protective gloves when mixing or using), 8 (Avoid breathing dust (or) vapour (or) spray mist)
b) when packed and labelled for the treatment of animals.	49 (WARNING – Do not mix with other medication except on veterinarian's advice)	1 (Avoid contact with eyes), 4 (Avoid contact with skin), 5 (Wear protective gloves when mixing or using), 8 (Avoid breathing dust (or) vapour (or) spray mist)

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DIMETHYL SULFOXIDE

cross reference: COPPER SALICYLATE, METHYL SALICYLATE

Schedule 6
Schedule 4
Appendix E, Part 2
Appendix F, Part 3

Implementation date: 1 February 2019

Reasons:

The delegate has amended the Schedule 4 proposal in the interim decision to ensure consistency with restrictions that apply to the use of DMSO in listed medicines, and confirms that the reasons for the final decision align with the reasons for the interim decision.

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

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

DMSO has a number of therapeutic uses due to its low toxicity, although it is an eye and skin irritant in undiluted form. However, as a carrier or universal solvent that enhances the skin penetration of other substances, DMSO enhances their therapeutic and toxic effects.

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

DMSO is widely used as a commercial solvent, and has many applications in agricultural and veterinary products. It is also found in a number of human therapeutic preparations, including for dermal use, at concentrations greater than 10%. The amendment to the Schedule 4 entry allows consistency with restrictions that apply to the use of DMSO in listed medicines. DMSO is prohibited in cosmetic products in the EU (Regulation (EC) No 1223/2009 – Annex II).

Only non-therapeutic uses of DMSO are covered by the proposed Schedule 6 exemption.

c. the toxicity of a substance:

DMSO is of low acute toxicity but is considered both a skin and eye irritant at concentrated

doses. It is a mild irritant to skin and eyes when diluted (less than 66 percent solutions). DMSO is not considered to be genotoxic or carcinogenic, nor to produce reproductive or developmental toxicities. In experimental animals, very high intravenous doses produced toxic effects in the liver and kidney, but no adverse effects on the liver or kidney have been observed in humans. Long-term oral or dermal administration produces only slight toxicity. The proposed exposure to DMSO is not a health concern.

DMSO enhanced dermal penetration of other compounds and may thereby enhance toxicity of these compounds.

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

- Schedule 6 products require labelling and packaging in accordance with the Poisons Standard. Labelling of unscheduled products is the responsibility of the manufacturer / supplier.
- The acute toxicity data supports a cut-off for DMSO in Schedule 6. Although the toxicity data presented by the applicant corresponds to DMSO concentrations of 60% and greater, 10% is a conservative and therefore reasonable estimate to ensure no significant toxicity in exempt preparations.

e. the potential for abuse of a substance:

- Scheduling history reports abuse in the 1980s but no recent reports and risk appears low.

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

- The intention of the Schedule 4 amendment is to align this entry with the requirements of the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2018.

Public submissions on the interim decision

No public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations.

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS, September 2018 – 2.2 Dimethyl sulfoxide (DMSO).

Scheduling proposal

The pre-meeting scheduling proposal for codeine was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

2.3. Aliphatic allyl esters

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to aliphatic allyl esters as follows:

Schedule 7 – Amend Entry

ALLYL ALCOHOL **except**

a) in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl ester; or

b) when separately specified in these Schedules.

Schedule 6 - New Entry

ALLYL ESTERS (excluding derivatives) being:

ALLYL CYCLOHEXANEACETATE (CAS No. 4728-82-9)

ALLYL CYCLOHEXANEPROPIONATE (CAS No. 2705-87-5)

ALLYL HEPTANOATE/ALLYL HEPTYLATE (CAS No. 142-19-8)

ALLYL HEXANOATE (CAS No. 123-68-2)

ALLYL ISOVALERATE (CAS No. 2835-39-4)

ALLYL NONANOATE (CAS No. 7493-72-3)

ALLYL OCTANOATE (CAS No. 4230-97-1)

ALLYL PHENYLACETATE (CAS No. 1797-74-6)

ALLYL TRIMETHYLHEXANOATE (CAS No. 68132-80-9)

in preparations containing 0.1 per cent or less of free allyl alcohol by weight of allyl ester **except** in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl esters.

Appendix J, Part 2

ALLYL ALCOHOL

Conditions for availability and use: 1 (Not to be available **except** to authorised or licensed persons).

Index – new entries

ALLYL ESTERS (excluding derivatives)

Schedule 6

ALLYL CYCLOHEXANEACETATE (CAS No. 4728-82-9)

Schedule 6

ALLYL CYCLOHEXANEPROPIONATE (CAS No. 2705-87-5)

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ALLYL HEPTANOATE/ALLYL HEPTYLATE (CAS No. 142-19-8)

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ALLYL HEXANOATE (CAS No. 123-68-2)

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ALLYL ISOVALERATE (CAS No. 2835-39-4)

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ALLYL NONANOATE (CAS No. 7493-72-3)

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ALLYL OCTANOATE (CAS No. 4230-97-1)

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ALLYL PHENYLACETATE (CAS No. 1797-74-6)

Schedule 6

ALLYL TRIMETHYLHEXANOATE (CAS No. 68132-80-9)

Schedule 6

Implementation date: 1 February 2019

Reasons:

The delegate has amended the interim decision after considering the public submission, and confirms that the reasons for the final decision align with the reasons for the interim decision.

Additional reasons for the final decision are the following:

· The scheduling of nine substances specifically (i.e. by CAS number) is preferred over an unqualified 'allyl esters' entry.

Public submissions on the interim decision

One (1) public submission was received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. The public submission opposed the proposal.

The main points provided in opposition of the amendment were:

· The scheduling of the 9 substances specifically (i.e. by CAS number) is preferred over an unqualified 'allyl esters' entry.

· The 5% concentration limit proposed for allyl esters does not align with overseas restrictions, higher concentrations of use would not necessarily pose risks to public health for these different use patterns i.e. domestic products not intended for direct skin contact.

- Align with overseas standards i.e. the requirement to ensure the level of free allyl alcohol is less than 0.1%.
- Proposed an amendment to delete 5% cut-off and include specific entries for all 9 allyl esters

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS, September 2018 – 2.3 Aliphatic allyl esters.

Scheduling proposal

The pre-meeting scheduling proposal for codeine was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

2.4. Astodrimer sodium

Delegate's final decision

The delegate's final decision under regulation 42ZCZR of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to astodrimer sodium as follows:

Schedule 3 – New Entry

ASTODRIMER SODIUM **except** in a condom lubricant.

Appendix F, Part 1 – New Entries

109	See your healthcare provider if you consider that you may be at risk of a Sexually Transmitted Infection (STI).
110	See a doctor if you plan to become pregnant, or are breastfeeding or plan to breastfeed

Appendix F, Part 3 – New Entry

ASTODRIMER SODIUM

Warning statements: 63, 64, 69, 75, 109, 110.

Appendix H – New Entry

ASTODRIMER SODIUM for the treatment and relief of bacterial vaginosis.

Index – New Entry

ASTODRIMER SODIUM

Schedule 3

Appendix F, Part 3

Appendix H

Implementation date: 1 February 2019

Reasons:

The delegate has amended the Appendix F warning statement in the interim decision after considering the public submission, and confirms that the reasons for the final decision remain the same as the reasons for the interim decision.

Public submissions on the interim decision

Two (2) public submissions were received before the second closing date in response to an invitation published on 10 September 2018 under regulation 42ZCZP of the Regulations. One submission was in support and one opposed the proposal.

The main points provided in opposition of the amendment were:

- A S2 entry would have been more appropriate
- Warning label 110 should be deleted as it is sufficiently covered by warning labels 64, 69, 109
- Amend warning label 111 to read 'See a doctor if you plan to become pregnant, or are breastfeeding or plan to breastfeed'

The main points provided in support of the amendment were:

- The S3 entry is better than the S4 entry originally proposed
- The substance may be suitable for S2 listing in the future
- Supports inclusion in Appendix H

Interim decision

The interim decision was published on the TGA website on 10 September 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS, September 2018 – 2.4 Astodrimer sodium.

Scheduling proposal

The pre-meeting scheduling proposal for codeine was published on the TGA website on 10 April 2018 at Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS.

Part B - Amendments to the Poisons Standard not referred to expert advisory committee

3. Delegate-only decisions on agricultural and veterinary chemicals

3.1. Benzovindiflupyr

Delegate's final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the Poisons Standard by creating a new Schedule entry for benzovindiflupyr as follows:

Schedule 6 – New Entry

BENZOVINDIFLUPYR

Index – New Entry

BENZOVINDIFLUPYR

Schedule 6

Implementation date: 1 February 2019

Delegate's considerations

The delegate considered the following in regards to this proposal:

- The application to amend the current Poisons Standard with respect to Benzovindiflupyr
- Section 52E (1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018)

Reasons:

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

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

Benzovindiflupyr is a broad spectrum foliar fungicide belonging to the succinate dehydrogenase inhibitor (SDHI) pyrazole carboxamide class. As a class, SDHI display a high selectivity for fungal mitochondrial complex II, with mammalian mitochondrial complex II being insensitive to the effects of these fungicides.

The risks of the proposed use of benzovindiflupyr are its moderate acute oral and inhalation toxicity and that it is moderately irritating to the eye.

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

Benzovindiflupyr has not been previously considered for scheduling. It is proposed to be used in an agricultural chemical product in Australia. It is a broad spectrum foliar fungicide belonging to the succinate dehydrogenase inhibitor (SDHI) pyrazole carboxamide class.

Benzovindiflupyr is approved for use in certain EU countries (100 g/L formulations) for the control of certain fungal diseases of wheat and barley. It has conditional registration in the US for use in a broader range of crops including corn, blueberries, cucurbit vegetables, cotton seed, legume vegetables, pome fruit, fruiting vegetables, turf and ornamentals. The overseas registrations are for a variety of other formulations and combinations with or without other active constituents, including propiconazole, prothioconazole, azoxystrobin, and difenoconazole.

c. the toxicity of a substance:

Benzovindiflupyr has moderate acute and inhalation toxicity and low acute dermal toxicity. It is a moderate eye irritant but not a skin irritant or sensitiser. It is not neurotoxic, genotoxic, carcinogenic, teratogenic or immunotoxic. The toxicity profile of benzovindiflupyr therefore supports inclusion in Schedule 6.

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

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new Schedule 6 entry for '*benzovindiflupyr*' in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

The applicant's reasons for the request are:

- The available toxicological data for benzovindiflupyr is considered to be sufficient for the purposes of recommending a scheduling decision.
- From the available data and international assessment reports, benzovindiflupyr has moderate acute oral and inhalation toxicity and low acute dermal toxicity. It is a moderate eye irritant but not a skin irritant or sensitiser. It is not neurotoxic, genotoxic, carcinogenic, teratogenic or immunotoxic. The toxicity profile of benzovindiflupyr supports consideration for listing in Schedule 6.
- Benzovindiflupyr, a fungicide, is approved for use in the EU and has conditional registration in the US. However, the formulated product proposed for registration in Australia has not been considered overseas. The EU considered an EC formulation (A15457H) containing 100 g/L benzovindiflupyr. Other formulations and combinations with/without a second active constituent have been registered overseas.

Current scheduling status

Benzovindiflupyr is not specifically scheduled in the current Poisons Standard and has not previously been considered for scheduling.

Scheduling history

Benzovindiflupyr is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Australian regulations

Benzovindiflupyr is not currently approved in Australia. The proposed product in Australia is an emulsifiable concentrate formulation containing the new active benzovindiflupyr (40 g/L) and the currently approved active propiconazole (250 g/L).

Benzovindiflupyr is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2018.

Benzovindiflupyr is neither an excipient nor active in any medicines on the ARTG.

International regulations

Benzovindiflupyr is approved for use in certain EU countries for the control of certain fungal diseases of wheat and barley. Conditional registration is established in the US with use in a broader range of crops including corn, blueberries, cucurbit vegetables, cotton seed, legume vegetables, pome fruit, fruiting vegetables, turf and ornamentals. The product proposed for registration in Australia is not currently registered elsewhere. Overseas registration is for a variety of other formulations, with or without other active constituents, including propiconazole, prothioconazole, azoxystrobin, and difenoconazole.

Substance summary

Benzovindiflupyr (ISO common name) is a broad spectrum foliar fungicide belonging to the succinate dehydrogenase inhibitor (SDHI) pyrazole carboxamide class.

Table 3.1: Chemical information for benzovindiflupyr

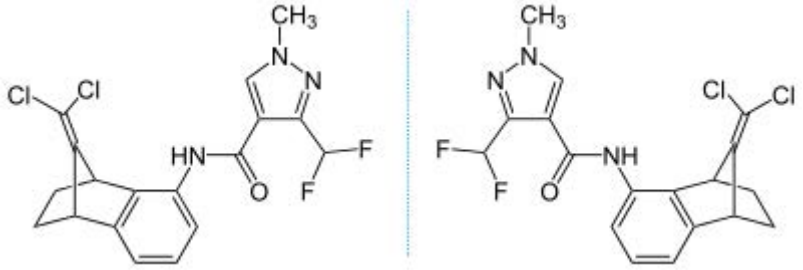
Property	Benzovindiflupyr	
Chemical structure (showing stereochemistry)		
	SYN546526 N-[(1S,4R)-9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide	SYN546527 N-[(1R,4S)-9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide
Molecular weight	398.2 g/mol	
Molecular formula	$C_{18}H_{15}Cl_2F_2N_{30}$	
CAS names	1072957-71-1	
IUPAC and/or common and/or other names	IUPAC: N-[(1RS,4SR)-9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide; CAS: 1H-pyrazole-4-carboxamide, N-[9-(dichloromethylene)-1,2,3,4- tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1- methyl Other: solatenol, benzovindiflupyr PubChem CID: 51347655; EC No. EC 691-719-4	

Table 3.2: Acute toxicity end-points for benzovindiflupyr

Toxicity	Species	Benzovindiflupyr	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	55	6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	5
Acute inhalational toxicity LC_{50} (mg/m^3/4 h)	Rat	>560	6
Skin irritation	Rabbit	Non-irritant*	-
Eye irritation	Rabbit	Moderate irritant	5
Skin sensitisation (LLNA)	Mouse	Non-sensitising	-

*JMPR classifies this as a mild irritant, GHS Category 3, based on slight erythema at 1 and 24 h observations. This category is not recognised by the EU, who classified this as non-irritant. APVMA classifies this as non-irritating, based on no dermal effects persisting until 72 hours.

Toxicity studies on benzovindiflupyr have been submitted to the APVMA in support of the active approval and have been reviewed by JMPR (2013)[5] and EFSA (2015),[6] the latter based on the EFSA Draft Assessment Report (2014). Studies on the product proposed to be registered in Australia have been submitted and were not considered by JMPR or EFSA. These studies will be assessed by the APVMA as part of the product evaluation at a later date.

Acute toxicity

Studies in rats done according to OECD guidelines show that benzovindiflupyr has moderate acute oral toxicity, low acute dermal toxicity, and moderate inhalation toxicity.

Skin and eye irritation

OECD guideline-compliant studies in rabbits show that benzovindiflupyr is not a skin irritant but is a moderate eye irritant.

Sensitisation

OECD guideline-compliant studies shows that benzovindiflupyr is not a skin sensitiser in the mouse local-lymph node assay (LLNA).

[5] BENZOVINDIFLUPYR 3–38 JMPR

[6] Conclusion on the peer review of the pesticide risk assessment of the active substance benzovindiflupyr, EFSA Journal 2015;13(3):4043

Repeat-dose toxicity

In repeat-dose oral toxicity studies in mice, rats and dogs, the main effects were on body weight and food consumption with minor findings in the liver. Repeat-dose dermal application resulted in no toxicity.

- In 28 and 90 day dietary studies in mice, the NOAEL was 100 ppm (16-17 mg/kg bw/d) based on body weight loss/reduced body weight gain at 300 ppm or higher.
- In 28 and 90 day dietary study in rats, the NOAEL was 100 ppm (9 mg/kg bw/d in the 28 day study and 7.6-8.2 mg/kg bw/d in the 90 day study) based on reduced body weight/body weight gain and food consumption at 400 ppm in the 28-d study and 750 ppm in the 90-d study.
- Dogs receiving doses up to 750 mg/kg bw/d in capsules for 13 weeks showed minimal findings from 375 mg/kg bw/d (reduced food consumption, loss of body weight/reduced body weight gain and minor clinical chemistry). The NOAEL was 30 mg/kg bw/d based on a >10% reduction in body weight gain.
- Repeat dose dermal application of benzovindiflupyr to rats for 28-d showed no systemic or local effects. The NOAEL was 1000 mg/kg bw/d, the highest dose tested.
- In an 80-week dietary study in mice, the NOAEL was 60 ppm (7.6 (M) and 8.7 (F) mg/kg bw/d) based on a LOAEL of 200pm for reduced body weight gain and an increased incidence of mucosal hyperplasia in the large intestine.
- In a 104-week dietary study in rats, the NOAEL was 100 ppm (4.9 (M) and 6.7 (F) mg/kg bw/d) based on a LOAEL of 400 (M) and 600 (F) mg/kg bw/d for reduced body weight gain and food consumption, and hepatic toxicity.
- In a 2-year dog study, capsule administration of benzovindiflupyr established a NOAEL of 250 mg/kg bw/d based on reduced body weight gain at 500 mg/kg bw/d.

Neurotoxicity

Neurotoxicity studies in rats were conducted as a single oral gavage dose of up to 10 mg/kg bw/d and dietary dosing over 90-days at doses up to 38 mg/kg bw/d. Benzovindiflupyr was not neurotoxic.

Carcinogenicity

Chronic studies in mice (diet; up to 200 ppm equal to 26 (M) and 29 (F) mg/kg bw/d), rats (diet; up to 400/600 ppm for F/M, equal to 30 (M) and 27 (F) mg/kg bw/d) and dogs (capsule; up to 500 mg/kg bw/d) demonstrated benzovindiflupyr is not carcinogenic. Tumours noted in rodent studies were determined not to be relevant to humans.

Genotoxicity

A range of *in vivo* and *in vitro* assays for genotoxicity indicated benzovindiflupyr is unlikely to be genotoxic.

Reproduction and developmental toxicity

No reproductive toxicity of benzovindiflupyr was observed in a multi-generation reproduction dietary study in rats at doses up to 250 ppm for females and 600 ppm for males. The parental and offspring NOAEL was 100 ppm (equal to 6.8 mg/kg bw/d for P generation males during pre-pairing and 7.8 mg/kg bw/d for F1 males during pre-pairing) based on reduced body weight

gain and food consumption, liver effects (adaptive/mild toxicity) and lower postnatal pup weights at 250 ppm in females (equivalent to 19.4 mg/kg bw/d for P generation females during pairing) and 600 ppm males (equal to 40.5 mg/kg bw/d for P generation males during pre-pairing). The NOAEL for direct effects on reproduction was the highest dose tested (250 ppm).

In an oral gavage developmental toxicity studies in rats and rabbits, benzovindiflupyr was not teratogenic. In rats, the maternal and foetal NOAEL was 15 mg/kg bw/d based on clinical signs, reduced food intake and body weight in dams and reduced weight and delayed ossification in foetuses at doses toxic to dams. The developmental NOAEL was 30 mg/kg bw/d, the highest dose tested. In rabbits, NOAEL for maternal, fetal and developmental effects was 35 mg/kg bw/d, the highest dose tested.

Immunotoxicity

Benzovindiflupyr did not show immunotoxic potential in a 28-day immunotoxicity study in mice at doses up to 400 ppm (equals 97 mg/kg bw/d) in the diet.

Summary

From the available data and the JMPR and EFSA12, 13 assessment reports, benzovindiflupyr has moderate acute oral and inhalational toxicity and low acute dermal toxicity. It is a moderate eye irritant but neither a skin irritant nor skin sensitiser. Health effects in animals given repeated doses primarily involved decreased body weight and body weight gain, effects on the liver and indications of general toxicity. It is not neurotoxic, genotoxic, carcinogenic, teratogenic or immuno-toxic. The toxicity profile of benzovindiflupyr supports consideration for listing in Schedule 6.

3.2. Dicyclanil

Delegate's final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the Poisons Standard Schedule 6 entry for dicyclanil as follows:

Schedule 6 – Amended Entry

DICYCLANIL except in preparations containing ~~5~~ 6.5 percent or less of dicyclanil.

Index

DICYCLANIL

Schedule 6

Implementation date: 1 February 2019

Materials considered

The delegate considered the following in regards to this proposal:

- The application to amend the current Poisons Standard with respect to dicyclanil
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E (1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance

Reasons:

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

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

Dicyclanil is an insecticide used for the prevention in blowfly strike in sheep. The risk profile of products containing 6.5 percent dicyclanil is considered to be very similar to that of products containing the same substance at a concentration of 5 percent.

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

Dicyclanil is an insect development inhibitor very specific for the prevention of blowfly strike in sheep. It does not control any other external parasites of sheep. It is used mainly as a spray-on. It is not used in other livestock, horses or pets.

c. the toxicity of a substance:

Dicyclanil 6.5 percent has low acute oral, dermal and inhalational toxicity, and is a slight skin and eye irritant. It is not considered to be a skin sensitiser. It is concluded based on the weight-of-evidence from in vitro and in vivo studies conducted since the original approval of dicyclanil that it is non-genotoxic.

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

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 6 entry for 'dicyclanil' in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

The applicant's reasons for the proposal were:

- Submitted toxicity data for the product [redacted] containing 6.5% dicyclanil, showed a similar hazard profile to an APVMA registered product, [redacted], containing 5% dicyclanil.
- [redacted] was considered by the NDPSC in 1997 for the purpose of establishing a 5% cut-off for dicyclanil from Schedule 6.
- The formulation details for [redacted] indicate that the product contains scheduled excipients but they are present at concentrations below their relevant cut-off levels.

Current scheduling status

Dicyclanil is currently in Schedule 6 of the Poisons Standard as follows:

Schedule 6

DICYCLANIL **except** in preparations containing **5 per cent or less** of dicyclanil.

Scheduling history

In November 1997, the National Drugs and Poisons Schedule Committee (NDPSC) considered a proposal to create a new entry for the new active consistent dicyclanil in the Poisons Standard. The committee agreed that the toxicological profile of dicyclanil was unremarkable and agreed that Schedule 6 was appropriate for dicyclanil. Whether products containing 5% or less of dicyclanil should be Schedule 5 or exempt from scheduling was equivocal but on balance the Committee agreed to exemption for these low concentrations.

Australian regulations

- Dicyclanil is an APVMA approved active constituent [redacted]
- [redacted] (50g/L) and [redacted] are APVMA approved products [redacted].
- Dicyclanil is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2018.
- Dicyclanil is neither an excipient nor active in any medicines on the ARTG.

International regulations

[redacted] (12.5 g/L) and [redacted] (50 g/L) and are registered in Europe (MRP registration in France, United Kingdom/Ireland, Netherlands, and Spain) and South Africa and [redacted] (65 g/L) is registered in the United Kingdom/Ireland.

[redacted] (12.5 g/L) and [redacted](65 g/L) are registered in New Zealand. ERMA Approval number: [redacted].

Dicyclanil is in the ECHA Annex III Inventory (EC / List no. 601-192-4)[7] as follows:

> *# Suspected carcinogen: The Toolbox profiler Carcinogenicity (genotox and nongenotox) alerts by ISS gives an alert for carcinogenicity; ISS Carcinogenicity model in VEGA (Q)SAR platform predicts that the chemical is Carcinogen (moderate reliability) # Suspected hazardous to the aquatic environment: The Danish QSAR database contains information indicating that the substance has a 48h EC50 to Daphnia of 1.44 mg/L; The Danish QSAR database contains information indicating that the substance has a 96h EC50 to green algae of 4.66 mg/L # Suspected mutagen: The Toolbox profiler in vitro mutagenicity (Ames test) alerts by ISS gives an alert for mutagenicity # Suspected persistent in the environment: The Danish QSAR database contains information indicating that the substance is predicted as non-readily biodegradable*

The maximum residue limited of dicyclanil in foodstuff according to EU regulation No. 37/2010[8] are as follows:

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions (according to Article 14(7) of Regulation (EC) No 470/2009)	Therapeutic Classification
Dicyclanil	Sum of dicyclanil and 2, 4, 6-triamino-pyrimidine-5-carbonitrile	Ovine	200 µg/kg 150 µg/kg 400 µg/kg 400 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Antiparasitic agents/Agents against ectoparasites

The sum total limit value to dicyclanil in wool is 2 ppm in the EU.[9]

[7] ECHA Annex III Inventory: 4,6-diamino-2-(cyclopropylamino)pyrimidine-5-carbonitrile

[8] COMMISSION REGULATION (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin

Substance summary

Dicyclanil is a pyrimidin derivative. Dicyclanil is an insect development inhibitor very specific for the prevention of blowfly strike in sheep. It does not control any other external parasites of sheep. It is used mainly as a spray-on. It is not used in other livestock, horses or pets.[10]

Table 2.1: Chemical information for dicyclanil

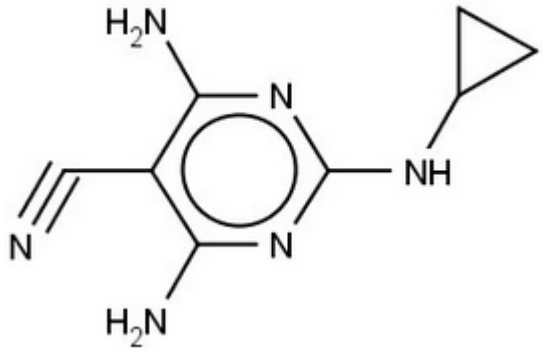
Property	dicyclanil
Chemical structure	
Molecular formula	$C_8H_{10}N_6$
CAS numbers	112636-83-6
IUPAC and/or common and/or other names	IUPAC: 4,6-diamino-2-cyclopropylaminopyrimidine-5-carbonitrile CAS: 4,6-diamino-2-(cyclopropylamino)-5-pyrimidinecarbonitrile

Table 2.2: Acute toxicity end-points for [redacted] and [redacted]

Toxicity	Species	End-point (6.5% product)*	End-point (5% product)**	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 (no deaths)	>5000 (no deaths)	S6 (for 6.5% product)* Nil (for 5% product)**

[9] COMMISSION DECISION establishing the ecological criteria for the award of the EU Ecolabel for textile products

[10] Paracitipedia.net - DICYCLANIL for veterinary use in SHEEP against blowfly strike and other cutaneous myiases

Toxicity	Species	End-point (6.5% product)*	End-point (5% product)**	SPF (2018) Classification
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000 (no deaths)	>5000 (no deaths)	Nil
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	No data	>3000 (estimate)	>3000 (estimate)	Nil
Skin irritation	Rabbit	Slight irritant	Slight irritant	Nil
Eye irritation	Rabbit	Slight irritant	Slight irritant	Nil
	BCOP test	Negative	-	
Skin sensitisation	Mouse (LLNA)	Negative	-	Nil
	GPMT		Negative	Nil

Studies on the product, [redacted] (6.5% dicyclanil), were provided to APVMA for assessment. The outcome is summarised below.

Acute toxicity

OECD guideline-compliant studies in rats [redacted] (6.5% dicyclanil), show that it has low acute oral toxicity, low acute dermal toxicity, and low inhalation toxicity.

Skin and eye irritation

OECD guideline-compliant studies in rabbits and in vitro in the BCOP test with [redacted] (6.5% dicyclanil) show it to be a slight skin and eye irritant.

Sensitisation

An OECD guideline-compliant murine LLNA test with [redacted] (6.5% dicyclanil) shows that it was not considered to be a skin sensitiser.

Genotoxicity

The APVMA has evaluated additional genotoxicity studies with the active constituent, dicyclanil (a new comet assay and a new micronucleus assay) together other genotoxicity studies that have been published since the original approval of dicyclanil in 1997. These studies do not alter the APVMA's previous conclusion that the weight-of-evidence indicates dicyclanil to be non-genotoxic and therefore do not impact on Scheduling considerations.