Publication of final decisions amending, or not amending, the current Poisons Standard

10 April 2018

Proposed amendments to the Poisons Standard referred to expert advisory committee

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

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

Pursuant to regulation 42ZCZK, the Secretary must invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice. Such a notice relating to the final decisions referred to herein was made available on the TGA website on 6 September 2017 and the opportunity to make submissions closed on 6 October 2017. 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#22, ACCS #21 and Joint ACMS-ACCS #17 meetings held in November 2017 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 November 2017 meetings of the Advisory Committee on Medicines Scheduling (ACMS #22), the Advisory Committee on Chemicals Scheduling (ACCS #21), and the Joint Advisory Committee on Medicines and Chemicals Scheduling (ACMS # 17) was made available on the TGA website on 2 February 2018 and closed on 5 March 2018. Public submissions received on or before this closing date will be published on the TGA website at 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*.

Proposed amendments to the Poisons Standard not referred to expert advisory committee

Subdivision 3D.3 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 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, 42ZCZO, 42ZCZU or 42ZCZW of the *Therapeutic Goods Regulations 1990*.

The final decisions to which this notice relates include decisions made with respect 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);
- scheduling proposals initially referred to the November 2017 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #21); and
- scheduling proposals on agricultural and veterinary chemicals, as well as new therapeutic Prescription Only medicines known as New Chemical Entities (NCEs) 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 advertising or marketing (e.g. logos or slogans associated with products), information about any alleged unlawful activity or that may be defamatory or offensive.

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

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.

Table of contents

Part A - Final decisions on matters referred to an expert advisory committee (November 2017)

1. Advisory Committee on Medicines Scheduling (ACMS #22)

1.1 Hyaluronic acid

Delegate's final decision

Final decision:
The delegate's final decision is to amend the Schedule 4 entry for hyaluronic acid as follows:

Schedule 4 – Amend Entry

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

Implementation date: **1 October 2019**
In view of the public submissions on the interim decision, the delegate has decided to delay the implementation date from 1 June 2018 to 1 October 2019.

Reasons:
The delegate notes the public submissions on the interim decision. However, as no new evidence has been received to alter the interim decision other than reconsidering the implementation date, the delegate has confirmed that the final decision and reasons for the final decision are identical to the interim decision.

Two public submissions on the interim decision suggested that supply of hyaluronic acid to doctors might have to be through a pharmacy, resulting in an increased cost to the patient. Making hyaluronic acid Schedule 4 for all injections or implantation would still allow the product to be directly supplied to the doctor and would not need to go through a pharmacy.

Public submissions on the interim decision

Three (3) public submissions were received that opposed the delegate's interim decision.

The main points opposed were:

- One submission acknowledged the delegate's rationale for the amendment to the Schedule 4 entry for hyaluronic acid to allow alignment with the existing subclause (e) of the Appendix A entry for medical devices. However, the proposal will not bring a positive benefit to the health of the Australian public and will not provide any additional risk reduction for patients. The reasons for the interim decision against the scheduling factors have confirmed the benefits of HA when used for its intended purpose and its lack of risks. Cosmetic or tissue augmentation use has a completely different benefit/risk framework, and is appropriately included in Schedule 4.
- Hyaluronic acid is not a dangerous drug.
- Based on consideration of the scheduling factors, the extensive experience of use in clinical practice and that the majority of supply already goes direct to the treating physician, the current method of product access is appropriate and does not pose any risks to public health that requires further mitigation.

- There was no consultation with stakeholders prior to this proposal being submitted. This step would have provided perspective on experience of use of the product in current clinical practice and an understanding of the impact on supply logistics and communication needs that would warrant a significantly longer transition time than indicated by the proposed implementation date of 1 June 2018.
- The implementation date of 1 June 2018 is unrealistic to allow for supply logistics, appropriate stakeholder communications, pack labelling changes. This could potentially lead to delaying or preventing market access to the products. A period of 12-18 months would be the minimum time period required.
- Hyaluronic acid products have been available for many years in other major markets including the EU, Canada and US. There are no restrictions on supply of the product and no evidence of any risk to public safety as a result of the current means of supply.
- The proposal is inconvenient for patients and may potentially increase costs for patients due to dispensing fees being incurred resulting in delayed access if the product is not routinely held in stock by the pharmacy, increased administrative burden for prescribers, and additional logistic impacts for wholesalers and suppliers.
- The product requires temperature control and currently is shipped from warehouse to temperature controlled clinics. Dispensing the product via a pharmacy to a patient could results in temperatures not being adequately controlled and increases the risk of the product being compromised. This in turn raises concerns for both the safety and efficacy of the product.
- Different hyaluronic acid products on the market are manufactured differently. Some products contain animal proteins that can cause adverse reactions to people who have allergies to avian products. There are concerns that these products may be perceived as biosimilar and may be substituted in the pharmacy.

Interim decision

The interim decision for hyaluronic acid was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.1. Hyaluronic acid.

Scheduling proposal

The pre-meeting scheduling proposal for hyaluronic acid was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.2 Cardarine

Delegate's final decision

Final decision:
The delegate's final decision is to include cardarine in Schedule 10 as follows:

Schedule 10 – New Entry

CARDARINE.

Index – New Entry

CARDARINE

Schedule 10

Implementation date: **1 June 2018**

Reasons:
As no new evidence has been received to alter the interim decision for cardarine, 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.

Interim decision

The interim decision for cardarine was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.2. Cardarine.

Scheduling proposal

The pre-meeting scheduling proposal for cardarine was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.3 Stenabolic (SR9009)

Delegate's final decision

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

Implementation date: **1 June 2018**

Reasons:
As no new evidence has been received to alter the interim decision for stenabolic and other synthetic REV-ERB agonists, 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.

Interim decision

The interim decision for Stenabolic (SR9009) was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.3. Stenabolic (SR9009).

Scheduling proposal

The pre-meeting scheduling proposal for Stenabolic (SR9009) was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.4 Ibutamoren

Delegate's final decision

Final decision:

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

Implementation date: **1 June 2018**

Reasons:

As no new evidence has been received to alter the interim decision for ibutamoren, 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.

Interim decision

The interim decision for ibutamoren was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.4. Ibutamoren.

Scheduling proposal

The pre-meeting scheduling proposal for ibutamoren was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

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

Delegate's final decision

Final decision:
The delegate's final decision is to create new Schedule 9 entries for alpha-pyrrolidinovalerophenone and methylone, and to amend the Schedule 9 entry for cathinone as follows:

Schedule 9 – New Entries

ALPHA-PYRROLIDINOVALEROPHENONE *(ALPHA-PVP).

METHYLONE *(MDMC).

Schedule 9 – Amend Entry

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

Index – New Entries

ALPHA-PYRROLIDINOVALEROPHENONE *(ALPHA-PVP)

Schedule 9

METHYLONE *(MDMC)

Schedule 9

Index – Amend Entry

CATHINONES
cross reference: SYNTHETIC CATHINONES

Schedule 9

Implementation date: **1 June 2018**

Reasons:
As no new evidence has been received to alter the interim decision for alpha-pyrrolidinovalerophenone, methylone and cathinones, 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.

Interim decision

The interim decision for alpha-pyrrolidinovalerophenone (alpha-PVP) and related substances methylone and synthetic cathinones was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.5. Alpha-Pyrrolidinovalerophenone (alpha-PVP) and related substances methylone and synthetic cathinones.

Scheduling proposal

The pre-meeting scheduling proposal for alpha-pyrrolidinovalerophenone (alpha-PVP) and related substances methylone and synthetic cathinones was published on the TGA website on

6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.6 Ibuprofen

Delegate's final decision

Final decision:

The delegate's final decision is not to amend the provisions of the Poisons Standard that relate to ibuprofen on the basis that the current Schedule 2 and Schedule 3 entries for ibuprofen remain appropriate.

Implementation date: **N/A**

Reasons:

The delegate has reviewed the public submissions on the interim decision for ibuprofen, which both supported and opposed the interim decision. No significant new evidence was received and most public submissions reiterated the submitter's initial public submissions to the invitation for public comment. In view of this, the delegate finds no reason to alter the interim decision and hence the delegate has confirmed that the final decision and reasons for the final decision are identical to the interim decision.

Additional comment:

The delegate has noted concerns on the labelling of ibuprofen products and will refer it to the appropriate area in TGA for their consideration.

Public submissions on the interim decision

Six (6) public submissions were received. Three (3) supported and three (3) opposed the delegate's interim decision.

The main points in support:

- The scheduling proposal does not articulate the problems it presumably seeks to address. Any increase in regulation should be based on sound and accurate evidence addressing concerns and scheduling changes are the only mechanism for addressing these concerns. Any regulatory decisions need to be consistent with the principles of best practice regulation.
- The overall risk benefit of ibuprofen remains positive and the safety profile is well established following the many years of experience with this medicine. There are no new publicly available safety concerns associated with ibuprofen and no evidence of excessive use, purchasing or harm through the current availability.
- The current Australian scheduling arrangements for ibuprofen are in line with other countries including the UK, Canada, USA and New Zealand. Ibuprofen has been available in Australia as an OTC medication for 30 years and in general retail for approximately 15 years, with limited reported adverse effects.
- The proposed scheduling change to ibuprofen has limited evidence that consumers would receive any benefit and it would have a significant impact on consumer choice and accessibility. It will also reduce competition and increase cost to consumers with no evidence of any incremental benefit provided. Ibuprofen is currently available from pharmacies in larger pack sizes and if required, allows consumers to obtain advice from pharmacists. There are considerable consumer benefits of retaining 24-hour availability of 24 pack sizes for acute pain, particularly in rural or remote areas or other communities that do not have access to pharmacies that are open after business hours.

- 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 RASML, which contains detailed mandatory warning statements in language that consumers are able to understand and act upon. There is a low propensity for toxicity in overdose and current labelling meets the RASML in relation to risks and complications of NSAIDs. Given the strong evidence, small packs of ibuprofen that are currently exempt can be appropriately selected and used by the reasonable consumer with acceptable safety.

- 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 did not identify any new safety concerns or risks and noted that there is minimal cardiovascular risk associated with ibuprofen when used at recommended OTC doses and duration.

The main points opposed:

- NSAIDs have a number of side effects which are dose related including major upper gastrointestinal bleeding, acute renal injury and cardiovascular effects. The benefits of keeping ibuprofen unscheduled do not outweigh the risks.

- Whilst ibuprofen is non-addictive there is a risk that consumers may intentionally or inadvertently take more than the recommended OTC dose and for much longer than the 4 day maximum especially if they are living with chronic pain. Studies show that people exceed the daily limit of ibuprofen and this risk could be mitigated by having ibuprofen only available in pharmacies. Further, there are concerns that continued availability of ibuprofen-containing products for self-selection through non-pharmacy settings has the potential to further increase the risk of adverse outcomes and may disadvantage people who are not achieving optimal pain management.

- Mandatory package labelling requirements do not adequately cover the risks associated with ibuprofen and RASML statements are not always effective. There is a lack of specific cautionary RASML labelling on ibuprofen sold in general stores about the risks of concomitant drug therapy, including the potential of renal "triple whammy" and antithrombotic drugs, increasing the risk of haemorrhage. Further, current labelling does not address the overall renal risks of NSAIDs in adults who are temporarily or otherwise at risk of renal failure caused by dehydration or fluid depletion. Even with the best designed label on the product packaging, pharmacists frequently report of instances where the patient has not read, not understood, misunderstood or disregarded information relevant to them to take the medicine safely or effectively when this information is not reinforced by the intervention of a pharmacist.

- The input of a health professional with knowledge of significant drug interactions is needed. When consumers are purchasing ibuprofen it is important for them to have access to professional guidance from pharmacists. Pharmacists are the health professionals that understand the well-established safety profile of ibuprofen for short term use and are most accessible to patients. They routinely encounter scenarios where ibuprofen and other NSAIDs are being used inappropriately or sub-optimally by individuals. Up-scheduling ibuprofen would provide the opportunity for pharmacist intervention, support a quality use of medicines approach to the use of ibuprofen, and contribute to enhanced patient care.

- There are a wide range of community pharmacies throughout Australia that are open for extended evening and public holiday hours. Recent expansion of discount pharmacy groups has also resulted in a very competitive environment regarding price and availability of non-prescription medications.

- There is accumulating evidence that taking ibuprofen regularly, in any dose, increases the risk of having an acute myocardial infarction.

Interim decision

The interim decision for ibuprofen was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.6. Ibuprofen.

Scheduling proposal

The pre-meeting scheduling proposal for ibuprofen was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.7 Melanotan II

Delegate's final decision

Final decision:
The delegate's final decision is to include melanotan II in Schedule 4 as follows:

Schedule 4 – New Entry

MELANOTAN II.

Index – New Entry

MELANOTAN II
cross reference: α–MELANOCYTE STIMULATING HORMONE

Schedule 4

Implementation date: **1 June 2018**

Reasons:
The delegate notes the public submission on the interim decision. As a Schedule 4 substance, there will still be the requirement for a medical practitioner to prescribe melanotan II. Any inappropriate prescribing by a medical practitioner would be regulated by the Medical Board of Australia.

The delegate has confirmed that the final decision and reasons for the final decision for melanotan II are identical to the interim decision.

Public submissions on the interim decision

One (1) public submission was received that opposed the delegate's interim decision and wanted melanotan II to go into Schedule 10.

The main points opposed are:

- Due to no benefits and well established public health risks including medication error, toxic effects, infection and false information around skin cancer protection with regards to sunless skin tanning increasing melanoma risk, melanotan II meets the criteria for Schedule 10.
- Schedule 4 is inappropriate as it would not provide the appropriate public access in consideration of its public health risks and will have no impact on current internet sales.
- Recent cases of overdose and poor injecting practices from online purchases highlight the current inappropriate public access, which will continue if it is listed as a Schedule 4 medicine and its continued availability through online pharmacies.

Interim decision

The interim decision for melanotan II was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.7. Melanotan II.

Scheduling proposal

The pre-meeting scheduling proposal for melanotan II was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.8 Orphenadrine

Delegate's final decision

Final decision:
The delegate's final decision is to not to amend the scheduling of orphenadrine.

Implementation date: **N/A**

Reasons:
As no new evidence has been received to alter the interim decision for orphenadrine, 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.

Interim decision

The interim decision for orphenadrine was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.8. Orphenadrine.

Scheduling proposal

The pre-meeting scheduling proposal for orphenadrine was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

1.9 Clotrimazole

Delegate's final decision

Final decision:
The delegate's final decision is to not to amend the Schedule 3 entry of clotrimazole.

Implementation date: N/A

Reasons:
The delegate notes the public submission on the interim decision. However, as no new evidence has been received to alter the interim decision for clotrimazole, 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

One (1) submission was received that opposed the delegate's interim decision.

The main points opposed are:

- The Schedule and Appendix entries for clotrimazole should be amended as proposed by the applicant. If not, the delegate will miss an opportunity to improve access to clotrimazole for the safe and effective treatment of thrush by women.
- Clotrimazole is available OTC without mandatory pharmacist intervention in more than 70 other countries and is available as a general sale item in the US and the UK. The delegate will also miss the opportunity to bring the Australian scheduling of clotrimazole into alignment with comparable overseas markets.

Interim decision

The interim decision for clotrimazole was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 1.9. Clotrimazole.

Scheduling proposal

The pre-meeting scheduling proposal for clotrimazole was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

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

2.1 Helium

Delegate's final decision

Final decision:

The delegate's final decision is that the Poisons Standard should not be amended to include helium on the basis that helium does not require scheduling.

Implementation date: N/A

Reasons:

The delegate notes the public submission on the interim decision. However, as no new evidence has been received to alter the interim decision for helium, 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

Three (3) public submissions were received, all in support of the interim decision.

The main points in support were:

- The interim decision to not schedule helium recognises the importance of helium in many industry sectors, the economic benefits of those sectors and the fact that the correct and legitimate use of helium does not meet the scheduling criteria.
- A thorough analysis was taken and a pragmatic outcome was achieved to ensure a balanced regulatory framework is maintained on helium.

Interim decision

The interim decision for helium was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 2.1. Helium.

Scheduling proposal

The pre-meeting scheduling proposal for helium was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

2.2 Salts of Boric Acid

Delegate's final decision

Final decision:

The delegates' final decision is to amend the Schedule 5 entry for boric acid align it with European Union concentrations for cosmetics and to create new entries in Schedule 5 for salts to address risks identified by IMAP assessment as follows:

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 ; or

d) in talc preparations containing 5% or less calculated as boron when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

e) in oral preparations containing 0.1% or less calculated as boron when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

f) in other preparations containing 3% or less calculated as boron when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS.

Index – Amend Entry

BORIC ACID
cross reference: BORAX, BORON

Schedule 5

Schedule 5 – New Entries

SODIUM BORATE (CAS No. 1330-43-4) **except**:

a) in talc preparations containing 5% or less of sodium borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

b) in oral preparations containing 0.1% or less of sodium borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN 3 YEARS OF AGE OR LESS; or

c) in other preparations containing 3% or less of sodium borate when labelled with a

warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS.

POTASSIUM BORATE (CAS No. 1332-77-0) **except**:

a) in talc preparations containing 5% or less of potassium borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

b) in oral preparations containing 0.1% or less of potassium borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN 3 YEARS OF AGE OR LESS; or

c) in other preparations containing 3% or less of potassium borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS.

MEA-borate (CAS No. 26038-87-9) **except**:

a) in talc preparations containing 5% or less of MEA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

b) in oral preparations containing 0.1% or less of MEA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN 3 YEARS OF AGE OR LESS; or

c) in other preparations containing 3% or less of MEA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS.

MIPA-BORATE (CAS No. 26038-90-4 and 68003-13-4) **except**:

a) in talc preparations containing 5% or less of MIPA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN 3 YEARS OF AGE OR LESS; or

b) in oral preparations containing 0.1% or less of MIPA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN 3 YEARS OF AGE OR LESS; or

c) in other preparations containing 3% or less of MIPA-borate when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF*

PRODUCT) IN CHILDREN 3 YEARS OF AGE OR LESS.

Index – New Entries

SODIUM BORATE (CAS No. 1330-43-4)

Schedule 5

POTASSIUM BORATE (CAS No. 1332-77-0)

Schedule 5

MEA-BORATE (CAS No. 26038-87-9)

Schedule 5

MIPA-BORATE (CAS No. 26038-90-4 and 68003-13-4)

Schedule 5

Implementation date: **1 June 2019**

The delegate notes the public submissions on the interim decision and agrees that an implementation date of 1 June 2018 is insufficient time to allow for relabelling and re-formulation of affected products. An implementation of 1 June 2019 will allow for any necessary labelling changes.

Reasons:

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

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

- Benefits:
  - Salts of boric acid are used as excipients to improve products.
- Risks:
  - Salts of boric acid are considered to have low to moderate effects in humans with normal use;
  - Salts of boric acid can cause minor human adverse effects with normal use;
  - Salts of boric acid requires caution in handling, storage, or use in alignment with the criteria for Schedule 5

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 domestic/industrial cleaning products (e.g dishwashing and laundry liquids), cosmetics, and personal products (e.g antiseptics, astringents, skin lotions, eyewash solutions), as well as enamels and glazes.

c) the toxicity of a substance:

- Studies show reproductive and developmental effects as a result of exposure to boric acid and its salts in sensitive animals.
  - Testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies.
- Sodium borate (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_{50}) in rats for the tested chemicals in the group and the analogue chemicals is >2000 mg/kg bw. The boric acid amine salts (MEA-borate and MIPA-borate) are also expected to have low acute oral toxicity (>2000 mg/kg bw).
- 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.
- 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.

Public submissions on the interim decision

Two (2) public submissions were received, both of which oppose the interim decision for salts of boric acid. The main points include:

- The interim decision appears to have no impact on the many complementary medicines which include borax below the 6 mg per daily dose cut-off. However, the proposed changes if implemented would affect products currently in the Australian market with an established history of safe use.
- There is no evidence that suggests immediate action is required for the risk management of these substances. An implementation date of 1 October 2018 is insufficient time for research, re-formulation, testing and relabelling of affected products. An adequate transition period of 12-30 months is requested.
- Amending the current Schedule 5 entry for boric acid may result in the inadvertent regulation of substances other than the 5 that were identified to be of concern in the IMAP assessment.
- The generic nature of proposed entry makes it difficult for industry to identify those substances which are intentionally captured, or those inadvertently captured by the proposed schedule entry. This has caused significant problems previously and continues to do so due to the derivatives issue.
- Scheduling of these 5 substances specifically (i.e. by CAS number) is preferred over an unqualified "all salts" entry and is consistent with addressing the risks identified for these 5 substances in the IMAP assessment.

- These substances are currently permitted for use in cosmetics in the EU 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". Alignment with the EU concentrations for cosmetics is preferred. If the proposed scheduling requirements are not aligned, changes to labelling and/or reformulation of products will be required.
- Other (non-cosmetic) products containing boric acid salts above 1% (such as metalworking fluids) will also go from being unscheduled to being Schedule 5 poisons.

Interim decision

The interim decision for salts of boric acid was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 2.2. Salts of Boric Acid.

Scheduling proposal

The pre-meeting scheduling proposal for salts of boric acid was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

2.3 Polihexanide

Delegate's final decision

Final decision:

The delegate's final decision is to amend the Schedule 6, Appendix F and index entries of the Poisons Standard for polihexanide as follows:

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

Implementation date: **1 June 2019**

The delegate notes the public submissions on the interim decision and agrees that an implementation date of 1 June 2018 is insufficient time to allow for relabelling and re-formulation of affected products. An implementation of 1 June 2019 will allow for any necessary labelling changes.

Reasons:

The delegate notes the public submissions on the interim decision, and confirms that the final decision and reasons for the final decision for polihexanide are identical to the interim decision. However, the implementation date has been amended from 1 June 2018 to 1 June 2019 to allow for any necessary labelling changes.

Public submissions on the interim decision

Two (2) public submissions were received, both in support of the interim decision for polihexanide.

The main points in support were:

- Polihexanide is included in the TGA's Permitted Ingredients list and in the TGA eBS ingredients list; it is allowed as an excipient in over the counter and listed medicines for topical dermal use, in a concentration of 0.3% or less. The Delegate's interim decision to align the Schedule 6 entry with this 0.3% limit will therefore have no impact on the scheduling of therapeutic goods.

- The interim decision is in line with Annex V of the EU Cosmetics Regulation "List of preservatives allowed in cosmetic products" which allows a maximum in-use concentration of 0.3% polihexanide.
- There will be no impact on non-cosmetic preparations as the current 5% exemption for non-cosmetic products is retained.
- Inclusion of synonyms in the index with cross-reference to the polihexanide schedule entry will provide clarity.

Regarding the implementation date:

  - There is no evidence that suggests immediate action is required for the risk management of these substances.
  - An implementation date of 1 June 2018 is insufficient time to allow for relabelling and re-formulation of affected products. An adequate transition period of at least 12 months (1 June 2019) is requested.

Interim decision

The interim decision for polihexanide was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 2.3. Polihexanide.

Scheduling proposal

The pre-meeting scheduling proposal for polihexanide was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

2.4 Cimicoxib

Delegate's final decision

Final decision:
The delegate's final decision is to create a new Schedule 4 entry for cimicoxib as follows:

Schedule 4 – New Entry

CIMICOXIB.

Implementation date: **1 June 2018**

Reasons:
As no new evidence has been received to alter the interim decision for cimicoxib, 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 submissions were received.

Interim decision

The interim decision for cimicoxib was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 2.4. Cimicoxib.

Scheduling proposal

The pre-meeting scheduling proposal for cimicoxib was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3. Advisory Committee on Chemicals Scheduling (ACCS #21)

3.1 Fluralaner

Delegate's final decision

Final decision:
The delegate's final decision is to amend the current Schedule 5 entry for fluralaner as follows:

Schedule 5 – Amend Entry

FLURALANER.

Index – Amend Entry

FLURALANER
cross-reference: CARBAMOYL BENZAMIDE PHENYL ISOXAZOLINE

Schedule 5

Implementation date: **1 June 2018**

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

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

- Benefit: fluralaner shows longer-lasting flea and paralysis tick prevention compared to other available products.
- Risks: there is uncertainty around the human exposure risk and indirect exposure from contact with treated animals.

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

- Spot-on flea treatments are in wide use and the public are familiar with the application process.

b) the toxicity of a substance:

- Fluralaner has a sufficiently low acute toxicity profile to be consistent with the Schedule 5 criteria of the Scheduling Policy Framework.

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

- Nil

d) the potential for abuse of a substance:

- Nil

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

- Nil

Public submissions on the interim decision

One (1) public submission was received that opposed the interim decision for fluralaner.

The main points opposed were:

- The recommendations of the Australian Pesticides and Veterinary Medicines Authority (APVMA) in its final Human Health Risk Assessment Technical Report are consistent with a Schedule 5 entry.
- A Schedule 5 entry is consistent with the scheduling of other members of the isoxazoline class and other currently registered topical parasiticides for pets.
- The assessment of human exposure risk and indirect exposure from contact with treated animals, for which the APVMA has now completed its evaluation, does not support inclusion in Schedule 4.
- The new topical formulation proposed does not present additional risks over the existing oral formulation.
- The new data and new formulation provide no reason to depart from the previous scheduling decision including because:
  - the toxicology package continues to indicate that fluralaner has a sufficiently low acute toxicity profile to be consistent with Scheduling Policy Framework criteria for listing in Schedule 5;
  - the proposed presentation for the topical fluralaner product continues to support an assessment that acute poisoning risk to humans (in particular children) is low; and
  - there is no basis to consider that treatment with the proposed topical fluralaner product requires the oversight of a veterinarian, whether in diagnosis or management of treatment.
- The proposed scheduling, while different from some international jurisdictions (as was recognised in the October 2014 scheduling decision for fluralaner), remains appropriate in Australia when the context of the different regulations and regulatory frameworks is taken into account.

Interim decision

The interim decision for fluralaner was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.1. Fluralaner.

Scheduling proposal

The pre-meeting scheduling proposal for fluralaner was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.2 Metofluthrin

Delegate's final decision

Final decision:

The delegate's final decision is to amend the Schedule 5 entry for metofluthrin by removing the phrase "*for use as a mosquito repellent*" from subclause (b) 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.

Implementation date: **1 June 2018**

Reasons:

As no new evidence has been received to alter the interim decision for metofluthrin, 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.

Interim decision

The interim decision for metafluthrin was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.2. Metafluthrin.

Scheduling proposal

The pre-meeting scheduling proposal for metafluthrin was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.3 Alpha-cypermethrin

Delegate's final decision

Final decision:

The delegate's final decision is to amend the Schedule 6 entry for alpha-cypermethrin by increasing the permitted concentration of alpha-cypermethrin from 25% to 30% in aqueous preparations as follows:

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.

Implementation date: **1 June 2018**

Reasons:

As no new evidence has been received to alter the interim decision for alpha-cypermethrin, 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.

Interim decision

The interim decision for alpha-cypermethrin was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.3. Alpha-cypermethrin.

Scheduling proposal

The pre-meeting scheduling proposal for alpha-cypermethrin was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.4 Silver Oxide

Delegate's final decision

Final decision:

The delegate's final decision is not to schedule silver oxide and to include it in Appendix B of the Poisons Standard as follows:

Appendix B – New Entry

SILVER OXIDE

Reasons for Entry: b (Use pattern restricts hazard)
Areas of Use: 7.14 (Spa/pool sanitiser)

Implementation date: **1 June 2018**

Reasons:

The delegate notes the public submission on the interim decision. However, as no new evidence has been received to alter the interim decision for silver oxide, 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

One (1) public submission was received, which supported the interim decision. The main point in support was that there are no unintended effects on the regulatory status of other silver compounds and/or derivatives which may be used in other sectors.

Interim decision

The interim decision for silver oxide was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.4. Silver Oxide.

Scheduling proposal

The pre-meeting scheduling proposal for silver oxide was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.5 1-Deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives

Delegate's final decision

The delegate has decided to set aside the final decision for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives pending wider review on the scheduling of surfactants.

Public submissions on the interim decision

Two (2) public submissions were received for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10- 16 acyl derivatives, one (1) in support and one (1) opposed.

The main point in support was:

- 1-Deoxy-1-(methylamino)-D-glucitol *N*-C10- 16 acyl derivatives is not entered in the TGA eBS ingredients list, nor is it entered in the TGA Permitted Ingredients List. The Delegate's interim decision will therefore have no impact on the scheduling of therapeutic goods.

The main points opposed were:

- Several surfactant substances were recently found not to require scheduling (including docusate sodium, sodium α- olefin sulfonates and sodium alkyl sulfates). It is imperative that a consistent, evidence-based approach is applied to the consideration of surfactant substances.
- Consideration of this substance for scheduling imposes stricter unnecessary controls on new, less hazardous surfactants when compared with older chemicals such as the lauryl sulfate salts.
- The risks of surfactants are already well managed. The public have a good understanding that surfactant-based products such as shampoos, soaps and detergents are irritating to skin and eyes and will instinctively rinse their eyes in case of accidental contact, without being prompted by the label. In fact, if accidental eye contact did occur, attempting to read any instructions on the product label at that stage may prove to be problematic.
- The NICNAS secondary notification report does not identify any significant public health risks that would require risk management through scheduling of these substances.
- The scheduling of surfactants is out of step with international requirements.
- The level of regulatory intervention for these low risk substances is disproportionate. Scheduling will result in extensive compliance activities for manufacturers including re-packaging and re-labelling, including the signal heading 'POISON', as well as other storage and handling requirements.
- Given the low risk presented by these products it is confusing for consumers when trying to reconcile the actual level of risk of using a product, when such 'POISON' warnings are carried by much more hazardous products.
- The scheduling of these substances should be considered in the context of the lauryl sulfate salts entry. As sodium lauryl sulfate (SLS) is known to be one of the harshest surfactants in use, there should be higher concentration cut-offs for less hazardous substances such as 1-deoxy-1-(methylamino)-D-glucitol *N*-C10- 16 acyl derivatives.
- A longer transition period of at least 12 months – i.e. an implementation date of 1 June 2019 at the earliest – is requested.
  - The proposed implementation date only allows 2 months from the date of final decision publication. This is inadequate to accommodate any changes required to the labelling and/or reformulation of products.
  - Any changes would 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 these substances.
- A wider review of the scheduling of surfactant substances is supported.

Interim decision

The interim decision for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.5. 1-Deoxy-1-(methylamino)-d-glucitol N-C10-16 acyl derivatives.

Scheduling proposal

The pre-meeting scheduling proposal for 1-deoxy-1-(methylamino)-D-glucitol *N*-C10-16 acyl derivatives was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.6 Phenyl methyl pyrazolone

Delegate's final decision

Final decision:

The delegate's final decision is to create a new Schedule 6 and Appendix E and F entries for phenyl methyl pyrazolone 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 warning statements to the following effect:

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).

Implementation date: **1 June 2019**

Reasons:

The delegate notes the public submissions on the interim decision. However, as no new evidence has been received to alter the interim decision for phenyl methyl pyrazolone, the delegate has confirmed that the final decision and reasons for the final decision are identical to the interim decision. However, the implementation date has been amended from 1 June 2018 to 1 June 2019 to allow for any necessary labelling changes.

Public submissions on the interim decision

Two (2) public submissions were received for phenyl methyl pyrazolone, both in support of the interim decision.

The main points in support were:

- Phenyl methyl pyrazolone is not entered in the TGA eBS ingredients list, nor is it entered in the TGA Permitted Ingredients List. The Delegate's interim decision will therefore have no impact on the scheduling of therapeutic goods.
- Regarding international alignment and labelling requirements:
  - Aligning the scheduling controls for phenyl methyl pyrazolone when used in cosmetics with those of the EU is supported.

- It is important to harmonise any warning statements and safety directions as much as possible with those required in the EU given that the vast majority (if not all) hair dye products in Australia are imported. While the proposed warning statements in the proposed Schedule 6 entry for phenyl methyl pyrazolone are consistent with those for other Schedule 6 hair dye substances, changes to existing labels will nevertheless be required as current labels generally follow the EU labelling requirements. Given the extensive nature of the labelling already required for these products under the EU regulation, and the similarity of the EU warnings with the intent of those proposed, there should be flexibility in the Schedule entry to allow "words to the effect of" rather than mandating the warning statements verbatim. This flexible approach is already well established in the Poisons Standard both within specific "reverse scheduling" entries as well as in Appendix E and F where it is noted that "Standard statements specified in this Appendix may be varied provided that the intent is not changed."

- Regarding implementation:
  - If the interim decision is implemented without change, a transition period of at least 24 months is required to allow for labelling changes. Any changes would affect products currently in the Australian market with an established history of safe use.
  - There is no evidence to suggest immediate action is required for the risk management of this substance.

Interim decision

The interim decision for phenyl methyl pyrazolone was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.6. Phenyl methyl pyrazolone.

Scheduling proposal

The pre-meeting scheduling proposal for phenyl methyl pyrazolone was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.7 Dinotefuran

Delegate's final decision

Final decision:
The delegate's final decision is to amend the current Schedule 5 entry for dinotefuran as follows:

Schedule 5 – Amend Entry

DINOTEFURAN **except** in preparations containing 1 per cent or less of dinotefuran.

Implementation date: **1 June 2018**

Reasons:
As no new evidence has been received to alter the interim decision for dinotefuran, 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.

Interim decision

The interim decision for dinotefuran was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.7. Dinotefuran.

Scheduling proposal

The pre-meeting scheduling proposal for dinotefuran was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

3.8 Afidopyropen

Delegate's final decision

Final decision:

The delegate's final decision is to create a new Appendix B entry for afidopyropen in the Poisons Standard as follows:

Appendix B – New Entry

AFIDOPYROPEN.

Reasons for Entry: b (Use pattern restricts hazard)
Areas of Use: 1.2 (Insecticide)

Implementation date: **1 June 2018**

Reasons:

As no new evidence has been received to alter the interim decision for afidopyropen, 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.

Interim decision

The interim decision for afidopyropen was published on the TGA website on 5 February 2018 at Scheduling delegates' interim decisions and invitation for further comment: ACCS/ACMS, November 2017 – 3.8. Afidopyropen.

Scheduling proposal

The pre-meeting scheduling proposal for afidopyropen was published on the TGA website on 6 September 2017 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017.

Part B - Final decisions on matters not referred to an expert advisory committee

4. Delegate-only decisions on agricultural and veterinary chemicals

4.1 *Bacillus amyloliquefaciens* MBI 600

Delegate's final decision

Final decision:

The delegate's final decision is to amend the current Appendix B entry for *Bacillus amyloliquefaciens*, strain QST 713 to remove '*strain QST 713*'; thereby creating a group entry for all *Bacillus amyloliquefaciens* strains and capturing both strain QST 713 and MBI 600. The amended Appendix B and Index entries are as follows:

Appendix B – Amend Entry

BACILLUS AMYLOLIQUEFACIENS

Date of entry: June 2018
Reason for entry: a (Low Toxicity).
Areas of use: 1.3 (fungicide).

Index – Amend Entry

BACILLUS AMYLOLIQUEFACIENS
cross reference: BACILLUS SUBTILIS, STRAIN QST 713; BACILLUS AMYLOLIQUEFACIENS, STRAIN MBI 600

Appendix B, Part 3

Implementation date: **1 June 2018**

Reasons:

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

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

- Benefits: *B. amyloliquefaciens* is a ubiquitous bacterium found in water, soil, air, decomposing plant material, on fresh produce and is widely used for the production of enzymes and specialty chemicals.
- Risks: Risks posed by *B. amyloliquefaciens* strains are very low. There may be a small risk to groups susceptible to infection.

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

- There are a range of benefits for preventing fungal disease in certain food crops.

c) *the toxicity of a substance:*

- The toxicity of strain MBI 600 is essentially identical to strain QST 713 which, in July 2017, was considered by the delegate not to require control by scheduling (Appendix B) due to the low

risk of infectivity, pathogenicity and low toxicity.

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

– *Bacillus amyloliquefaciens* is a naturally occurring microorganism with very low infectivity, low pathogenicity and a low risk of causing skin irritancy.

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

In November 2017, the Australian Pesticides and Veterinary Medicines Authority (APVMA) submitted a proposal to not include *Bacillus amyloliquefaciens* MBI 600 in any schedule. A consideration should be given to creating a generic entry for all *B. amyloliquefaciens* strains in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

The applicant's reasons for the request are:

- *B. amyloliquefaciens* is a ubiquitous bacterium found in water, soil, air, decomposing plant material, on fresh produce and is widely used for the production of enzymes and specialty chemicals. *B. amyloliquefaciens* MBI 600 is described as being antagonistic towards fungal plant pathogens via nutrient competition, site exclusion and colonisation.
- The acute toxicity profile for *B. amyloliquefaciens*, strain MBI 600 is essentially identical to strain QST 713 with the oral LD_{50} being >109 viable spores/rat, the dermal LD_{50} >5050 mg/kg bw in rats (or >2 x 109 cfu/kg bw in rabbits) and the inhalational LC_{50} being >5310 mg/m3/4 h. There was no evidence of pathogenicity or infectivity in the lungs following intratracheal inoculation and lethality by intravenous administration is low (LD_{50} >107 spores). *B. amyloliquefaciens* MBI 600 was not a skin irritant but was a slight eye irritant (probably as a result of the size of the bacillus bacteria) and a skin sensitiser in the guinea pig maximisation test. However, since *B. amyloliquefaciens* MBI 600 is unable to penetrate the skin barrier due to its size this GPMT result is likely to be a false positive. A Buehler assay, which is better suited to detect sensitisation for occupational exposure, was not performed on the active constituent but was negative for the formulated product.
- The acute toxicity profile of the formulated product (11% *B. amyloliquefaciens* MBI 600) was low following oral, dermal and inhalational routes of administration. The formulated product was not irritating or sensitising to the skin (Buehler) but it was a slight eye irritant possibly due to abrasive nature of one of the excipients.
- *B. amyloliquefaciens* MBI 600 was negative in an Ames test for mutagenicity.
- Repeat dose toxicity, carcinogenicity, reproductive toxicity, developmental toxicity and neurotoxicity studies were not performed as it was a microbial preparation.

Current scheduling status

Bacillus amyloliquefaciens MBI 600 is not currently scheduled.

Bacillus amyloliquefaciens strain QST 713 will be included in Appendix B (Reasons: a, low toxicity; Area of Use: 1.3 fungicide) in the 1 February 2018 update of the Poisons Standard.

Scheduling history

Bacillus amyloliquefaciens MBI 600 is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Bacillus amyloliquefaciens strain QST 713 was considered by the ACCS in July 2017. The Committee recommended *B. amyloliquefaciens* strain QST 713 to be included in Appendix B. The reasons for the recommendation were that:

- The risks posed by *B. amyloliquefaciens* strain QST 713 are very low. There may be a small risk to groups susceptible to infection;
- That there are a range of benefits for preventing fungal disease in certain food crops;
- *B. amyloliquefaciens* is a naturally occurring microorganism with very low infectivity, low pathogenicity and a low risk of causing skin irritancy. The risks should be mitigated by personal protective equipment worn on mixing/loading and application in accord with APVMA labels; and
- Worker data shows that *B. amyloliquefaciens* strain QST 713 is unlikely to be a respiratory sensitiser.

The delegate accepted the committee advice and agreed to place *B. amyloliquefaciens* in Appendix B on 1 February 2018.

Australian regulations

Bacillus amyloliquefaciens MBI 600 does not appear to be in any products on the Australian Register of Therapeutic Goods (ARTG).

Bacillus amyloliquefaciens MBI 600 does not appear in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2017

Bacillus amyloliquefaciens MBI 600 is not currently approved by the APVMA.

International regulations

- **USA:** *B. amyloliquefaciens* MBI 600 (antecedent Bacillus subtilis MBI 600) was registered in 1994 with the US EPA; *B. amyloliquefaciens* strain D747 was registered in 2011; and *B. amyloliquefaciens* strain PTA-4838 was registered in 2017. The US EPA lists *Bacillus amyloliquefaciens* MBI 600 is exempt for pesticide chemical residues in food, including residues resulting from post-harvest uses, when applied or used in accordance with good agricultural practices.
- **EU:** *B. amyloliquefaciens* MBI 600 was approved in September 2016, in accordance with EC No 1107/2009 and EU No 540/2011, at a minimum purity of 5.0×10^{14} CFU/kg. Member States were instructed to pay particular attention to the protection of workers and operators due to *B. amyloliquefaciens* being considered to be a potential sensitiser.

Substance summary

A structural diagram has not been provided as *Bacillus amyloliquefaciens* MBI 600 is a whole organism.

Acute Toxicity

Table 4.1.1: Acute toxicity end-points for *Bacillus amyloliquefaciens*

Toxicity	Species	*Bacillus amyloliquefaciens MBI 600*	SPF* Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5000	-
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5050	-
Acute inhalational toxicity LC_{50} (mg/m^3)	Rat	>5310	-
Skin irritation	Rabbit	None	-
Eye irritation	Rabbit	Slight	5
Skin sensitisation (GPMT)	Guinea pig	Positive	6

*Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015)

Repeat-dose toxicity

Repeat dose toxicity studies were not conducted based on the absence of findings in the acute toxicology and infectivity/pathogenicity studies. This is reasonable and appropriate for a non-pathogenic biological active ingredient of this type.

Genotoxicity

No evidence of genotoxicity have been shown to be produced by *B. amyloliquefaciens.*

Carcinogenicity

No information was available.

Reproduction and developmental toxicity

No information was available.

Clinical observations

EFSA conducted a review update of the safety concerns for the Qualified Presumption of Safety (QPS) status of biological agents that are added intentionally to food and animal feeds including *Bacillus* species (EFSA, 2013). The observations reported and summarised in the QPS document were considered clinically relevant to the current assessment and addressed reports of claims where *B. amyloliquefaciens* was a causative agent in clinical cases. The relevant QPS review text is presented below (with minor edits). Collectively, there was no substantive new evidence that confirmed that *B. amyloliquefaciens* was the causative agent in the clinical reports and also confirmed the existing EFSA position of non-toxigenic/non-pathogenic potential of *B. amyloliquefaciens* towards humans.

'In total, 230 articles found by relevant search terms were screened. A bacteraemia related to a pacemaker wire infection was caused by *B. licheniformis* (Idelevich *et al.,* 2012). *B. amyloliquefaciens* and *B. licheniformis* were identified as the cause of a bacteraemia in a patient with an oesophageal perforation (La Jeon *et al.,* 2012). Kim *et al.,* (2012) reported a case of bacteraemia caused by *B. licheniformis* following vertebrotherapy in a patient with a lung cancer. Safety concerns for food producing animals were also considered in the search because 'the body of knowledge about the organisms for which QPS is sought must be sufficient to provide adequate assurance that any potential to produce adverse effects in humans, livestock or the wider environment is understood and

predictable' (EFSA, 2007). A *Bacillus sp.* was isolated from abscesses in several sheep and goats, but authors could not identify the isolates to the species level by phenotypic tests and sequence of 16s rRNA gene (Mariappan *et al.,* 2012). Gangrenous mastitis in several goats was caused by *Bacillus spp.,* one of the isolates was identified *B. cereus*, but other isolates were not identified at the species level (Mavangira *et al.,* 2013). *B. amyloliquefaciens* was isolated, together with *staphylococcus*, from milk of goats with subclinical mastitis (Razi *et al.,* 2012), but without evidence that *B. amyloliquefaciens* was the cause of the mastitis.

These infections in humans were linked to specific predisposing factors and did not suggest a risk for the consumer *via* exposure through the food and feed chain. The abscesses reported in sheep were not sufficiently characterised to determine whether *Bacillus* species from the QPS list were involved. In respect to the report of mastitis in goats, the co-isolation of *S. aureus*, a well-known agent of mastitis, raised doubt regarding the role of *B. amyloliquefaciens* in the infection.

Public exposure

A review article on foodborne illness(es) caused by *Bacillus* species, including some QPS *Bacillus* species was published in 2012 (Logan, 2012). The outcomes of the review were in line with the previous QPS assessment (EFSA, 2008) concerning the rare implication of QPS *Bacillus* species in foodborne illnesses, and the likely implication of peptidolipides with toxic activities produced by the responsible strains. Two articles described some biological activities of peptidolipides with biosurfactants produced by *B. amyloliquefaciens*. A biosurfactant produced by a strain of *B. amyloliquefaciens* caused epithelium cell vacuolisation and microvilli damage in the midgut of an insect larvae (LC_{50} approx. 200 ng/mg according to Ghribi *et al.,* 2012) and a *B. amyloliquefaciens* strain isolated from a Korean fermented soybean paste produced up to 48 mg surfactin per kg in the fermented food, and the surfactin inhibited growth of human breast cancer cells (IC_{50} 10 µg/mL, Lee *et al.,* 2012)."

The applicant identified a range of clinically relevant publications in which *B. amyloliquefaciens* was associated with a range of disease manifestations (Ochoa, 2015, Aoki *et al.,* 2015; Baur & Bakehe, 2014; Hong *et al.,* 2008; Inomata *et al.,* 2007; Long *et al.,* 2014; Pavic *et al.,* 2005; Stickel *et al.,* 2008). Collectively, these publications identified *B. amyloliquefaciens* as being present along with other possible co-causative agents. The case subjects (human and domestic/farm animals) often had pre-existing conditions or a reasonable likelihood of compromised immune system function. *B. amyloliquefaciens* was not identified as being associated with a clinical condition in the citations and no citation suggested an association between *B. amyloliquefaciens* with genotoxic, carcinogenic or reproductive toxicity potential. Broadly, the citations were consistent with the EFSA QPS review summary discussed above.

Please refer to the HHRA technical report for further information on the toxicology of *Bacillus amyloliquefaciens*.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2018)
- Other relevant information

Delegate's final decision

The delegate's final decision to be implemented on **1 June 2018** is to amend the current Appendix B entry for *Bacillus amyloliquefaciens*, strain QST 713 to remove the phrase 'strain QST 713' thereby creating a group entry for all *Bacillus amyloliquefaciens* strains and capturing both strain QST 713 and MBI 600. The amended Appendix B and Index entries are as follows:

Appendix B – Amend Entry

BACILLUS AMYLOLIQUEFACIENS

Date of entry: June 2018
Reason for entry: a (Low Toxicity).
Areas of use: 1.3 (fungicide).

Index – Amend Entry

BACILLUS AMYLOLIQUEFACIENS
cross reference: BACILLUS SUBTILIS, STRAIN QST 713; BACILLUS AMYLOLIQUEFACIENS, STRAIN MBI 600

Appendix B, Part 3

Reasons for the final decision:

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

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

- Benefits: *B. amyloliquefaciens* is a ubiquitous bacterium found in water, soil, air, decomposing plant material, on fresh produce and is widely used for the production of enzymes and specialty chemicals.
- Risks: posed by *B. amyloliquefaciens* strain MBI 600 are very low. There may be a small risk to groups susceptible to infection.

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

- There are a range of benefits for preventing fungal disease in certain food crops.

c) the toxicity of a substance:

- The toxicity of strain MBI 600 is essentially identical to strain QST 713 which, in July 2017, was considered by the delegate not to require control by scheduling (Appendix B) due to the low risk of infectivity, pathogenicity and low toxicity.

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

- *Bacillus amyloliquefaciens* is a naturally occurring microorganism with very low infectivity, low pathogenicity and a low risk of causing skin irritancy.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

4.2 *N,N*-Dimethyloctanamide and *N,N*-dimethyldecanamide

Delegate's final decision

Final decision:
The delegate's final decision is to create new Schedule 6 entries for *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide. as follows:

Schedule 6 – New Entries

N,N-DIMETHYLOCTANAMIDE.

N,N-DIMETHYLDECANAMIDE.

Implementation date: **1 June 2019**

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

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

- Benefit: use in Agvet products.
- Risks: there is uncertainty around the human exposure risk.

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

- *N,N*-dimethyldecanamide and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide have been identified in recent formulations of agricultural chemical products in Australia.
- Uses include as solvents in emulsifiable concentrate type agricultural chemical products, as well as coating, industrial cleaning, and processing aids.

c) *the toxicity of a substance:*

- Based on the available toxicity data, a Schedule 6 entry is considered appropriate due to severe skin and eye irritation and acute toxicological endpoints.

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:*

- *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide have not previously been considered for scheduling.

Applicant's scheduling proposal and reasons for proposal

In November 2017, the Australian Pesticides and Veterinary Medicines Authority (APVMA) submitted a proposal to create new Schedule 6 entries for "*N,N*-dimethyloctanamide, *N,N*-dimethyldecanamide; and mixtures thereof" in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

The applicant's proposed amendments to the Poisons Standard are:

Schedule 6 – New Entry

FATTY ACID DIMETHYLAMIDE MIXTURES.

The applicant's reasons for the request are:

- *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide have been identified in pesticides products.
- The available toxicological data for *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide show that they are severe eye and skin irritants.

Current scheduling status

N,N-dimethyloctanamide, *N,N*-dimethyldecanamide; and mixtures thereof, are not scheduled.

Scheduling history

N,N-dimethyloctanamide, *N,N*-dimethyldecanamide are not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

The analogue dimethylacetamide (DMAC) is in Schedule 5 and Schedule 6 of the Poisons Standard.

In February 1997, the National Drugs and Poisons Schedule Committee (NDPSC) considered an application to list DMAC in the SUSMP due to its use in veterinary and agricultural products. DMAC is well absorbed through skin, gastrointestinal tract and lungs. Toxicological studies of DMAC mainly showed eye irritancy, hepatotoxicity, as well as some gestational and developmental toxicity at high exposures. The committee delayed a decision to seek public consultation on the matter and at the May 1997 meeting. Due to no responses made to the gazette notice, the committee decided to include DMAC in Schedule 6 with a cut-off of 20% or less to Schedule 5.

Australian regulations

N,N-dimethyloctanamide and *N,N*-dimethyldecanamide are listed with no additional information in the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework to accelerate the assessment of existing chemicals on the Australian Inventory of Chemical Substances (AICS).

N,N-dimethyloctanamide and *N,N*-dimethyldecanamide are not listed in Safe Work Australia Hazardous Chemical Information System (HCIS).

N,N-dimethyloctanamide and *N,N*-dimethyldecanamide do not appear to be in any products on the Australian Register of Therapeutic Goods (ARTG).

N,N-dimethyloctanamide and *N,N*-dimethyldecanamide do not appear in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2017

International regulations

- **USA:** *N,N*-dimethyldecanamide and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide are approved for use in the USA as ingredients in agricultural products.
- **EU:** *N,N*-dimethyloctanamide is registered with REACH. Based on the classification provided by companies to ECHA, GHS hazard statements have been established in Europe for registrations in REACH of *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide.
  - The same GHS hazard statements apply to both *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide – H315: causes skin irritation; H319: causes serious eye irritation

Substance summary

Table 4.2.1: Chemical information for *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide

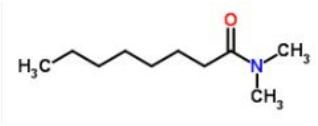
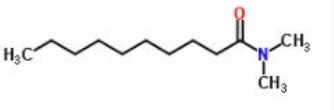
Property	*N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide
Chemical structures	 171.28 g/mol  199.33 g/mol
Molecular formulas	$C_{10}H_{21}NO$ and $C_{12}H_{25}NO$
CAS names	*N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide
CAS numbers	1118-92-9 and 14433-76-2
IUPAC and/or common and/or other names	IUPAC: *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide Alternative names of *N,N*-dimethyloctanamide include: *N,N*-dimethylcaprylamide; and octanamide, *N,N*-dimethyl Alternative names of *N,N*-dimethyldecanamide include: *N,N*-dimethylcapramide; decanamide, *N,N*-dimethyl; *N,N*-dimethyldecanoamide; and *N,N*-dimethyldecan-1-amide Commercial names of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide mixtures include "Hallcomid® M-8-10", and "Agnique KE 3658"

Table 4.2.2: Acute toxicity end-points for "Hallcomid-M-8-10", a commercial mixture of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide

Toxicity	Species	Hallcomid-M-8-10	SPF (2015) Classification[1]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1250 or 1770	6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	$400 < LD_{50} < 2000$	6
Acute inhalational toxicity LC_{50} (mg/m³/4h)	Rat	> 3550	-
Skin irritation	Rabbit	Severe irritant	6
Eye irritation	Rabbit	Severe irritant	6
Skin sensitisation (Buehler)	Guinea pig	Not sensitising	-

The APVMA has identified *N,N*-dimethyldecanamide and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide in recent formulations of agricultural chemical products. These fatty acid

[1] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

dimethylamide compounds are used as solvents in emulsifiable concentrate type agricultural chemical products. Other uses of these compounds may include coating, industrial cleaning, and processing aids.

The APVMA has sourced publically available toxicological data on *N,N*-dimethyldecanamide, *N,N*-dimethyloctanamide, and mixes of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide. The main available studies were conducted on the commercial product "Hallcomid M-8-10", which contains 40-70% *N,N*-dimethyloctanamide (*w/w*) and 30-60% *N,N*-dimethyldecanamide (*w/w*). The US EPA website was the main source of information (*e.g.:* US EPA 2003b: Dossier and Robust summaries for CAS N°: 1118-92-9: https://ofmpub.epa.gov/oppthpv/document_api.download?FILE=c14154rr.pdf).

Both *N,N*-dimethyldecanamide and *N,N*-dimethyloctanamide; and commercial mixtures of these constituents appear to have similar toxicity.

Acute toxicity based on US EPA reports

In rat, Hallcomid M-8-10 has low acute oral and inhalational toxicity but moderate acute dermal toxicity.

Skin and eye irritation

Hallcomid M-8-10 is a severe skin irritant in rabbits.

Hallcomid M-8-10 is considered to be a severe eye irritant in rabbits (irreversible corneal opacity). On animal welfare grounds observations were terminated 4 days after instillation of the test material. If observations had been allowed to progress, a corrosive effect may have been observed.

Sensitization

Hallcomid M-8-10 was not a skin sensitiser in Guinea pig (Buehler test, induction with 5% test material in 80% ethanol, challenge with 2.5% test material in acetone).

Repeat-dose toxicity based on US EPA reports

In a 5-day inhalation toxicity study, rats were exposed to aerosolised Hallcomid M-8-10 for 6 hours/day (nose/head only) and observed for two weeks post-exposure. Autopsies were performed after killing the animals either on Day 7, or on Day 22. The NOAEL was ~111 mg/m^3, based on clinical signs of toxicity (laboured breathing, bradypnea, wheezing, reduced mobility, reddened nose and serous nasal discharge), decreased body temperatures, and histopathological findings in the respiratory tract in both sexes (increased incidence of (*i*) goblet cell hyperplasia in the nasal mucosa of females on days 7 and 22, (*ii*) subpleural round-cell infiltration of the lungs in males, and (*iii*) marginal emphysema of the lungs) at the highest dose of ~521 mg/m^3.

In a 6 weeks oral gavage toxicity study in dogs, which significance was likely impaired by infection, the NOAEL was 100 mg/kg bw/d, based on transient behavioural changes (lateral position, disturbed coordination, and prone position) observed in some animals after dosing at 1000 mg/kg bw/d.

In a 90-day dietary toxicity study in rats, the NOAEL was ~137 mg/kg bw/d in males and ~895 mg/kg bw/d (the highest dose used in the study) in females, based on an increased incidence/severity of renal basophilic cortical tubules (which was reversible during a 28 days additional observation period) and deposition of protein casts in medullary tubules of kidneys in males at the highest dose of 788 mg/kg bw/d.

Mutagenicity and Genotoxicity

In an adequate range of *in vitro* assays conducted on bacteria and mammalian cells, there was no evidence that Hallcomid M-8-10 is mutagenic or genotoxic.

Reproduction and developmental toxicity

Hallcomid M-8-10 was administered to presumed pregnant rats by oral gavage at 0, 50, 150 or 450 mg/kg bw/d on GD6 to GD15. The maternal NOAEL was 150 mg/kg bw/d, with a LOAEL of 450 mg/kg bw/d based on ruffled fur, ventral recumbency, dyspnea, apathy, transient comatose, reduced bodyweight gain as a result of decreased food consumption. The embryo/foetal NOAEL was

150 mg/kg bw/d, with a LOAEL of 450 mg/kg bw/d based on increased post-implantation loss, decreased bodyweight and increased incidence of skeletal malformations (incomplete or non-ossification of the vertebrae and sternebrae). It was considered that the observed treatment related effects on reproductive and developmental parameters were likely due to maternal toxicity.

Hallcomid M-8-10 (in 0.5% cremophor) was administered to presumed pregnant rabbits by oral gavage at 0, 100, 300, or 1000 mg/kg bw/d on GD6-GD18. No treatment related signs of toxicity were observed and gross necropsies were all unremarkable. Reproductive parameters were unaffected by the treatment. Maternal food consumption and bodyweight gain of the highest dose group were slightly lower than controls. The maternal NOAEL was 300 mg/kg bw/d, with a LOAEL of 1000 mg/kg bw/d based on reduced bodyweight gain. The embryo/foetal NOAEL was 1000 mg/kg bw/d, the highest tested dose.

Considering both studies, Hallcomid M-8-10 (*N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide) appears to be non-teratogenic in rats or rabbits, and there was no indication that these compounds may affect reproductive parameters in the absence of maternal toxicity.

Toxicity of formulated products containing N,N-dimethyldecanamide and/or mixes of N,N-dimethyloctanamide and N,N-dimethyldecanamide

Acute toxicity studies were conducted with three formulated agricultural products containing either 52% *N,N*-dimethyldecanamide or 39-47% mixes of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide. These studies indicate that the products have low acute oral, dermal and inhalational toxicity, and are slight skin irritants. One of these products is a skin sensitiser while the two other products are not skin sensitisers. These three products are all severe eye irritants.

Eye irritancy of the products was largely attributed to *N,N*-dimethyldecanamide, or mixes of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide present in the products' formulations, as (*i*) these compounds are known severe eye irritants and (*ii*) based on the known toxicity of other constituents, it appears unlikely that they contributed significantly to the eye irritancy of the formulated products.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- Section 52E of the Therapeutic Goods Act 1989
- Scheduling Policy Framework (SPF 2018)
- Other relevant information

Delegate's final decision

The delegate's final decision to be implemented on **1 June 2019** is to create new Schedule 6 entries for *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide. as follows:

Schedule 6 – New Entries

N,N-DIMETHYLOCTANAMIDE.

N,N-DIMETHYLDECANAMIDE.

Reasons for the final decision:

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

a) <u>the risks and benefits of the use of a substance:</u>

– Benefit: use in Agvet products

- Risks: there is uncertainty around the human exposure risk

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

- *N,N*-dimethyldecanamide and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide have been identified in recent formulations of agricultural chemical products in Australia.
- Uses include as solvents in emulsifiable concentrate type agricultural chemical products, as well as coating, industrial cleaning, and processing aids.

c) the toxicity of a substance:

- Based on the available toxicity data, a Schedule 6 entry is considered appropriate due to severe skin and eye irritation and acute toxicological endpoints.

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:

- *N,N*-dimethyldecanamide, and mixtures of *N,N*-dimethyloctanamide and *N,N*-dimethyldecanamide have not previously been considered for scheduling.

4.3 Etofenprox

Delegate's final decision

Final decision:
The delegate's final decision is not to schedule etofenprox and to create an Appendix B entry as follows:

Appendix B – New Entry

ETOFENPROX

Reason for listing: a (Low Toxicity)
Area of use: 1.2 (Insecticide)

Implementation date: **1 June 2018**

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

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:

– Etofenprox is a pyrethroid-like insecticide, which has activity via contact or ingestion against a range of insect pests and is used for insecticidal control in crops including canola, cabbage, grapes, peach and apples.

c) the toxicity of a substance:

– Etofenprox has low acute toxicity and is not a skin or eye irritant and is not a skin sensitiser in animal studies.

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:

– Etofenprox is not currently scheduled in Australia.

Applicant's scheduling proposal and reasons for proposal

In November 2017, the Australian Pesticides and Veterinary Medicines Authority (APVMA) submitted a proposal not to include etofenprox in any schedule 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 etofenprox is considered to be sufficient for the purposes of recommending a scheduling decision.

- The Advisory Committee on medicines Scheduling (ACCS) may consider that the toxicity hazard profile for acute exposure to etofenprox does not warrant a schedule.
- Etofenprox is available in the European Union (EU) as an agricultural insecticide.
- Etofenprox is a non-ester pyrethroid insecticide with comparable toxicity and a similar mode of action to other pyrethroids.
- ACCS has never previously considered a non-ester type pyrethroid insecticide.

Current scheduling status and scheduling history

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

Australian regulations

Etofenprox is not currently approved in Australia.

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

Etofenprox does not appear in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2017

International regulations

- **USA:** Etofenprox was listed as a pesticide by EPA in the USA in 2007 under the Federal Insecticide, Fungicide and Rodenticide Act (EPA-HQ-OPP-2007-0804).
- **Canada:** Etofenprox was granted full registration in Canada for the sale and use of etofenprox-containing products.
- **EU:** Etofenprox is approved for use by ECHA as a biocidal active substance with hazard classifications that etofenprox is very toxic to aquatic life, very toxic to aquatic life with long lasting effects and may cause harm to breastfed children.

Substance summary

Table 4.3.1: Chemical information for etofenprox

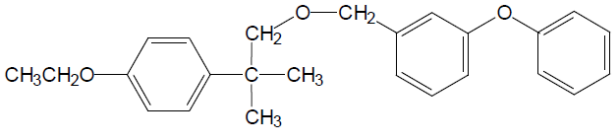
Property	Etofenprox
Chemical structure	 376.5 g/mol
Molecular formula	$C_{25}H_{28}O_3$
CAS names	1-[[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl]-3-phenoxybenzene
CAS numbers	80844-07-1
IUPAC and/or common and/or other names	2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether; ethofenprox; MTI-500

Table 4.3.2: Acute toxicity end-points for ETOFENPROX

Toxicity	Species	Etofenprox	SPF (2015) Classification[2]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat Dog	> 2000 > 5000	- -
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 2000	-
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	> 5880	-
Skin irritation	Rabbit	Not irritating	-
Eye irritation	Rabbit	Not irritating	-
Skin sensitisation (GPMT)	Guinea pig	Not sensitising	-

Etofenprox is a pyrethroid-like insecticide, which has activity *via* contact or ingestion against a range of insect pests. In the EU, the product has been approved for insecticidal control in many crops including rape (canola), cabbage, grapes, peach and apples.

Toxicology data on etofenprox were submitted with the application and have been assessed by ECHA/ EFSA, and publically available reports are available, including the EFSA review, and etofenprox Draft Assessment Reports (DAR) 2007. Following initial appraisal of the submission in 2003, further data were supplied and assessed in 2007-11 and 2016 to allow completion of EU registration. Etofenprox has been reviewed by JMPR (Etofenprox 184 – toxicology and residues).

Acute toxicity

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

Skin and eye irritation

OECD guideline-compliant studies in rabbits showed that etofenprox is not a skin or eye irritant.

Sensitisation

In an OECD guideline-compliant study, etofenprox was not a skin sensitiser using the guinea pig maximisation test.

Repeat-dose toxicity

In a 28-day dermal toxicity study in rabbits, the NOAEL was 1000 mg/kg bw/d, the highest dose tested.

The liver is a common target for toxicity in mouse, rat and dog. The liver, kidneys and haemo-lymphoreticular system were target organs in the mouse. The liver and thyroid gland were target organs in rats.

In a 90-day dietary toxicity study in mice, the NOAEL was 375 mg/kg bw/d, based on increased mortality and reduced body weight gain, minor haematological effects, histopathological alterations indicative of kidney damage, and minor changes in the liver at 1975 mg/kg bw/d.

In a 90-day dietary toxicity study in rats, the NOAEL was 20 mg/kg bw/d, based on liver toxicity (hepatocyte enlargement and clinical evidence of liver dysfunction affecting fat metabolism and

[2] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

synthesis of clotting factors) and thyroid toxicity (increased number of micro-follicles and reduced circulating T4) at 120 mg/kg bw/d.

In a 1-year dietary toxicity study in dogs, the NOAEL was 32.2 mg/kg bw/d, based on hepatotoxicity, including increased liver weights and histopathological alterations at 339 mg/kg bw/d. The effects were reversible.

Neurotoxicity

There was no evidence that etofenprox was neurotoxic in rats in an acute neurotoxicity study, or in a 13-week neurotoxicity study, or in a neurodevelopmental toxicity study.

Mutagenicity, Genotoxicity and Carcinogenicity

In an adequate range of *in vitro* and *in vivo* assays, there was no evidence that etofenprox is mutagenic, genotoxic or carcinogenic in mice and rats. JMPR concluded that etofenprox is unlikely to pose a carcinogenic risk to humans at dietary exposure levels.

Reproduction and developmental toxicity

No reproductive toxicity was observed in two multi-generation reproduction dietary studies in rats at doses up to 246 mg/kg bw/d or by gavage 5000 mg/kg bw/d by gavage. The NOAEL for parental toxicity was 37 mg/kg bw/d based on reduced body weight gain and histopathological findings in the liver, kidneys and thyroid at 246 mg/kg bw/d.

In two oral gavage developmental toxicity studies in rabbits, the overall NOAEL for developmental and maternal toxicity was 100 mg/kg bw/d based on reduced maternal body weight gain and feed consumption on the first day of dosing (gestation day 6), mortality and increased post-implantation loss at the high dose of 250 mg/kg bw/d.

JMPR concluded that etofenprox is not teratogenic in rats or rabbits.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2018)
- Other relevant information

Delegate's final decision

The delegate's final decision to be implemented on **1 June 2018** is not to schedule etofenprox and so create an Appendix B entry for etofenprox as follows:

Appendix B – New Entry

ETOFENPROX

Reason for listing: a (Low Toxicity)
Area of use: 1.2 (Insecticide)

Reasons for the final decision:

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

a) <u>the risks and benefits of the use of a substance:</u>

– Nil.

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

- Etofenprox is a pyrethroid-like insecticide, which has activity via contact or ingestion against a range of insect pests and is used for insecticidal control in crops including canola, cabbage, grapes, peach and apples.

c) the toxicity of a substance:

- Etofenprox has low acute toxicity and is not a skin or eye irritant and is not a skin sensitiser in animal studies.

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:

- Etofenprox is not currently scheduled in Australia.

4.4 Metamitron

Delegate's final decision

Final decision:
The delegate's final decision is to create a new Schedule 6 entry for metamitron as follows:

Schedule 6 – New Entry

METAMITRON.

Implementation date: **1 June 2018**

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

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:*

– Metamitron is a triazinone herbicide that acts by inhibiting photosynthesis.

c) *the toxicity of a substance:*

– Metamitron has moderate acute oral toxicity and low acute dermal and inhalational toxicity; it is not a skin or eye irritant and is not a skin sensitiser in animal studies.

– It is not neurotoxic, mutagenic, genotoxic, carcinogenic or teratogenic. The available toxicological data for metamitron supports its 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:*

– Metamitron is not currently scheduled in Australia.

– Metribuzin, a related trazinone herbicide in Schedule 6, has the same mode of action as metamitron.

Applicant's scheduling proposal and reasons for proposal

In November 2017, the Australian Pesticides and Veterinary Medicines Authority (APVMA) submitted a proposal to include METAMITRON in Schedule 6 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

The applicant's proposed amendments to the Poisons Standard are:

Schedule 6 – New Entry

METAMITRON.

The applicant's reasons for the request are:

- The available toxicological data for metamitron is considered to be sufficient for the purposes of recommending a scheduling decision.
- A related trazinone herbicide with the same mode of action as metamitron is metribuzin.
- From the available data and international assessment reports, metamitron has moderate acute oral toxicity and low acute dermal and inhalational toxicity. It is not a skin or eye irritant, and is not a skin sensitiser. It is not neurotoxic, mutagenic, genotoxic, carcinogenic or teratogenic. The toxicity profile of metamitron supports consideration for listing in Schedule 6.
- Metamitron, a herbicide, is approved for use in the EU. However, the formulated product evaluated in the EU in 2007 at the time of metamitron approval was a suspension concentrate (SC) containing 700 g/L metamitron.
- In 2015, registration of a granular (WG) 150 g/kg metamitron product (Brevis) was granted in the EU. This product is identical to the one proposed for registration in Australia.

Current scheduling status and scheduling history

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

Australian regulations

Metamitron is not currently approved in Australia.

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

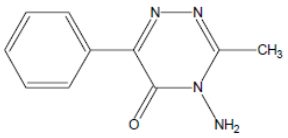
Metamitron does not appear in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2017

International regulations

- **EU**: Metamitron is registered with REACH (Annex III) and is approved for use in certain EU countries for the control of annual grasses and broad-leaved weeds.
- **NZ**: Metamitron is registered to the ACVM Act (No P7241) and is an approved pursuant to the HSNO Act (No HSR000535).
- **USA**: Metamitron is registered with the US FDA.

Substance summary

Table 4.4.1: Chemical information for metamitron

Property	Metamitron
Chemical structure	 Mol Wt 202.2 g/mol
Molecular formula	$C_{10}H_{10}N_4O$
CAS names	4-amino-3-methyl-6-phenyl-1,2,4-triazin-5(4*H*)-one

Property	Metamitron
CAS numbers	41394-05-2
IUPAC and/or common and/or other names	4-amino-4,5-dihydro-3-methyl-6-phenyl-1,2,4-triazin-5-one

Table 4.4.2: Acute toxicity end-points for metamitron

Toxicity	Species	Metamitron	SPF (2015) Classification[3]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1183	6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 4000	-
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	3910 (2 deaths)	5
Skin irritation	Rabbit	Not irritating	-
Eye irritation	Rabbit	Not irritating	-
Skin sensitisation (GPMT)	Guinea pig	Not a sensitiser	-

Metamitron is a triazinone herbicide that acts by inhibiting photosynthesis. Toxicity studies on metamitron and its product have been submitted to the APVMA in support of the active approval and product registration. These studies have been reviewed by EFSA and are described in the Draft Assessment Report, 2007. The DAR for metamitron is available.

Acute toxicity

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

Skin and eye irritation

OECD guideline-compliant studies in rabbits show that metamitron is not a skin or eye irritant.

Sensitisation

An OECD guideline-compliant study shows that metamitron is not a skin sensitiser in the guinea pig maximisation test.

Repeat-dose toxicity

The liver was the main target organ for metamitron toxicity in rodents and dogs, based on clinical chemistry parameters indicative of liver toxicity, organ weight and histopathological changes in the liver and effect on red blood cell parameters suggestive of anaemia.

In an 18-month dietary study in mice, the NOAEL was 7.1 mg/kg bw/d based on liver effects at dose levels of ≥ 35.9 mg/kg bw/d.

In a 2-year dietary toxicity study in rats, the NOAEL was 4.9 mg/kg bw/d based on changes in red blood cell parameters and liver toxicity including increased cholesterol, increased relative liver weights and histopathological changes in the liver at dose levels of ≥ 19.5 mg/kg bw/d.

[3] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

In a 1-year dietary toxicity study in dogs, the NOAEL was 1.1 mg/kg bw/d based on effects on haematology and clinical chemistry indicative of liver toxicity in mid- and high-dose animals treated at ≥ 13.6 mg/kg bw/d. In a 2-year dietary toxicity study in dogs, the NOAEL was 3.0 mg/kg bw/d based on increased cholesterol at dose levels of ≥ 11.3 mg/kg bw/d considered to be indicative of impaired liver function.

Neurotoxicity

There was no evidence that metamitron was neurotoxic.

Genotoxicity and Carcinogenicity

Overall, metamitron is not considered to be a genotoxic compound based on the weight of evidence from a range of *in vitro* and *in vivo* genotoxicity studies. Metamitron was not carcinogenic in rats receiving up to 81.5 mg/kg bw/d. Metamitron was not carcinogenic in mice up to 174 mg/kg bw/d.

Reproduction and developmental toxicity

No reproductive toxicity of metamitron was observed in two multi-generation reproduction dietary studies in rats. The NOAEL was 3.9 mg/kg/d based on decreased body weight gain in parents and offspring at 19.8 mg/kg/d. In the second study reduced numbers of corpora lutea and implantations were seen at the highest dose of 239 mg/kg/d. There was no evidence of reproductive toxicity at 97.2 mg/kg/d, which was the overall reproductive NOAEL. The overall parental and developmental NOAEL was 7.3 mg/kg/d based on reduced body weight gain in both studies and reduced pup survival in the second study.

In two oral gavage developmental toxicity studies in rats and one study in rabbits, metamitron was not teratogenic. The maternal and developmental NOAEL was 10 mg/kg bw/d and 100 mg/kg bw/d, respectively, based on reduced body weight gain at 100 mg/kg bw/d. In the oral gavage developmental toxicity study in rabbits, the maternal NOAEL was 40 mg/kg bw/d based on reduced body weight gain at 160 mg/kg bw/d. The developmental NOAEL was 160 mg/kg bw/d, the highest dose tested, based on lack of relevant findings.

Summary

From the available data and the EFSA assessment report, metamitron has moderate acute oral toxicity and low acute dermal and inhalational toxicity. It is not a skin or eye irritant, and is not a skin sensitiser. It is not neurotoxic, mutagenic, genotoxic, carcinogenic or teratogenic. The toxicity profile of metamitron supports consideration for listing in Schedule 6.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- Section 52E of the Therapeutic Goods Act 1989
- Scheduling Policy Framework (SPF 2018)
- Other relevant information

Delegate's final decision

The delegate's final decision to be implemented on **1 June 2018** is to create a new Schedule 6 entry for metamitron as follows:

Schedule 6 – New Entry

METAMITRON.

Reasons for the final decision:

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

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:

- Metamitron is a triazinone herbicide that acts by inhibiting photosynthesis.

c) the toxicity of a substance:

- Metamitron has moderate acute oral toxicity and low acute dermal and inhalational toxicity; it is not a skin or eye irritant and is not a skin sensitiser in animal studies.
- It is not neurotoxic, mutagenic, genotoxic, carcinogenic or teratogenic. The available toxicological data for metamitron supports its 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:

- Metamitron is not currently scheduled in Australia.
- Metribuzin, a related trazinone herbicide in Schedule 6, has the same mode of action as metamitron.

5. New Chemical Entities – medicines for human therapeutic use

5.1 Olaratumab

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for olaratumab in the Poisons Standard as follow:

Schedule 4 – New Entry

OLARATUMAB.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- It is a new chemical entity with no marketing experience in Australia.

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

c) the dosage, formulation, labelling, packaging and presentation of a substance
- Nil.

d) the toxicity 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.

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of olaratumab, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Olaratumab is a monoclonal antibody developed for the treatment of solid tumors. It is directed against the platelet-derived growth factor receptor alpha.

Olaratumab is used to treat soft-tissue sarcoma (STS).

Scheduling status

Olaratumab is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons

Standard March 2018 (SUSMP No. 20)), but as a monoclonal antibody, it is captured by the Schedule 4 entry for monoclonal antibodies as follows:

> **Schedule 4**
>
> MONOCLONAL ANTIBODIES for therapeutic use **except**:
>
> (a) in diagnostic test kits; or
>
> (b) when separately specified in these Schedules.

International regulations

Olaratumab is a prescription medicines in the EU and the USA. Olaratumab is a Schedule D prescription medicine in Canada.

Olaratumab is unclassified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors; and
- Orphan drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.2 Tezacaftor

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for tezacaftor in the Poisons Standard as follows:

Schedule 4 – New Entry

TEZACAFTOR.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- It is a new chemical entity with no clinical or marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- Tezacaftor will be used in combination with ivacaftor for the treatment of cystic fibrosis in patients who have the genotype for mutations known to be responsive to tezcaftor/ivacaftor.
- Tezacaftor will be prescribed by physicians with expertise in cystic fibrosis.

c) the toxicity of a substance
- There are no acute serious toxicities.

d) the dosage, formulation, labelling, packaging and presentation of a substance
- Tezacaftor is an oral medicine.

e) the potential for abuse of a substance
- Unlikely.

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

Scheduling proposal

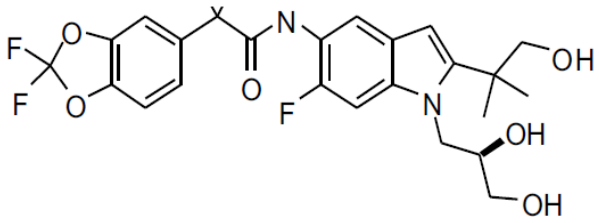
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of tezacaftor, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Tezacaftor is a *CFTR* corrector that acts directly on *CFTR* to treat the underlying cause of CF by improving the cellular processing and trafficking of *CFTR*, thereby increasing the quantity of functional *CFTR* at the cell surface.

Tezacaftor/ivacaftor as an orphan drug is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

Table 5.2.1: Chemical properties for tezacaftor

Property	Tezacaftor
Chemical structure	
IUPAC name	1-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5yl}cyclopropane-1-carboxamide
Empirical formula	$C_{26}H_{27}F_3N_2O_6$
Molecular weight	520.5 g/mol

Scheduling status

Tezacaftor is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

On 4 July 2014, the European Medicines Agency granted tezacaftor orphan drug designation for the treatment of cystic fibrosis.

Tezacaftor does not appear to be a scheduled substance in New Zealand, the USA or Canada.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report for orphan application (D17-3501202, D17-3501201); and
- The new drug application; (D17-3509315).

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.3 Benralizumab

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for benralizumab in the Poisons Standard as follows:

Schedule 4 – New Entry

BENRALIZUMAB.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- Benralizumab is a new chemical entity with no clinical or marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- There are other monoclonal antibodies selective for the IL-5 receptor used to treat eosinophilic asthma.
- The proposed indication for benralizumab is for add-on maintenance treatment for severe asthma in patients with an eosinophilic phenotype. It is likely to be prescribed mainly by respiratory specialists.

c) the toxicity of a substance
- Adverse events are not dose related. The main treatment emergent adverse events are hypersensitivity reactions, these are uncommon.

d) the dosage, formulation, labelling, packaging and presentation of a substance
- The recommended dose is 30 mg of benralizumab given by subcutaneous injection every 4 weeks for 3 doses then every 8 weeks.
- Each pack contains a single dose, single use, sterile pre-filled syringe.

e) the potential for abuse of a substance
- There is a low potential for abuse.

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

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of benralizumab, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Benralizumab is a humanised, afucosylated, monoclonal antibody selective for the alpha subunit of the human interleukin-5 receptor (IL-5Rα). Benralizumab is of the IgG1, kappa-class produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Benralizumab is indicated as an add-on maintenance treatment for severe asthma in patients with an eosinophilic phenotype.

Table 5.3.1: Identifiers, properties and naming of benralizumab

Property	Benralizumab
CAS Number	1044511-01-4
Molecular formula	$C_{6492}H_{10060}N_{1724}O_{2028}S_{42}$
Molecular weight	146.0 kg/mol
ANN/INN	eBS ID: 111153 INN: Benralizumab

Scheduling status

Benralizumab is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)), but as a monoclonal antibody, it is captured by the Schedule 4 entry for monoclonal antibodies as follows:

> **Schedule 4**
>
> MONOCLONAL ANTIBODIES for therapeutic use **except**:
>
> (a) in diagnostic test kits; or
>
> (b) when separately specified in these Schedules.

International regulations

Benralizumab is unclassified in New Zealand, Canada and USA.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.4 Glecaprevir

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for glecaprevir in the Poisons Standard as follows:

Schedule 4 – New Entry

GLECAPREVIR.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- Glecaprevir is a new chemical entity with no clinical/marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- Glecaprevir is to be used as an oral fixed dose combination tablet with pibrentasvir for the treatment of chronic hepatitis C infection in adults.

c) the toxicity of a substance
- The most common adverse effects observed in clinical trials were headache, fatigue and nausea.

d) the dosage, formulation, labelling, packaging and presentation of a substance
- The fixed dose combination tablets of glecaprevir co-formulated with pibrentasvir should be prescribed by medical professionals who are familiar with the management of viral hepatitis. The patients need to be instructed to follow the dosing regimens.

e) the potential for abuse of a substance
- Nil.

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

Scheduling proposal

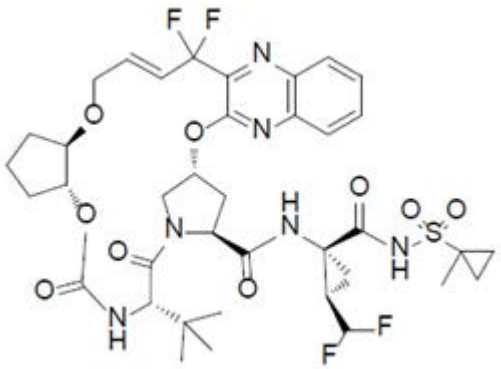
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of glecaprevir, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Glecaprevir is a pangenotypic inhibitor of the HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins), and is essential for viral replication. In a biochemical assay, glecaprevir inhibited the proteolytic activity of recombinant NS3/4A enzymes from clinical isolates of HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a with IC50 value ranging from 3.5 to 11.3 nM.

Glecaprevir, co-formulated with pibrentasvir, is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Table 5.4.1: Identifiers, properties and naming of glecaprevir

Property	Glecaprevir
CAS Number	1365970-03-1
Chemical structure	
Molecular formula	$C_{38}H_{46}F_4N_6O_9S$ (anhydrate)
Molecular weight	838.9 g/mol (anhydrate)
Chemical name/s	(3a*R*,7*S*,10*S*,12*R*,21*E*,24a*R*)-7-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1*H*,10*H*-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide hydrate
ANN/INN	eBS ID: 111184 AAN and INN - glecaprevir

Scheduling status

Glecaprevir is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

Glecaprevir is approved in the USA as a prescription medicine.

Glecaprevir is unclassified in New Zealand and Canada.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.5 Pibrentasvir

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for pibrentasvir in the Poisons Standard as follows:

Schedule 4 – New Entry

PIBRENTASVIR.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- Pibrentasvir is a new chemical entity with no clinical/marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- Pibrentasvir co-formulated with glecaprevir is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

c) the toxicity of a substance
- Reported adverse events from clinical trials include headache, fatigue, and nausea.

d) the dosage, formulation, labelling, packaging and presentation of a substance
- The fixed dose combination tablets pibrentasvir co-formulated with glecaprevir should be prescribed by medical professionals who are familiar with the management of viral hepatitis. The patients need to be instructed to follow the dosing regimens.

e) the potential for abuse of a substance
- Nil.

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

Scheduling proposal

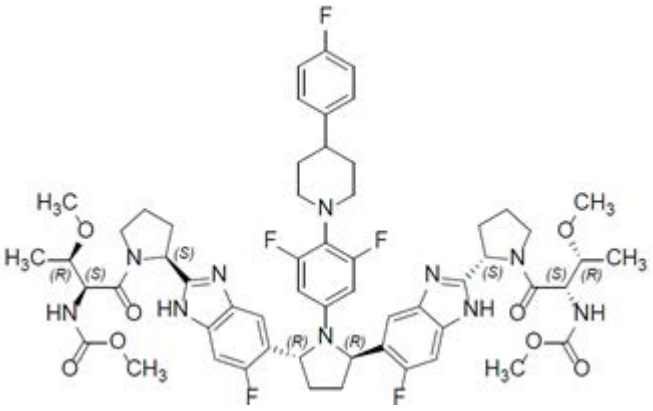
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of pibrentasvir, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Pibrentasvir is a pangenotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of pibrentasvir has been characterised based on cell culture antiviral activity and drug resistance mapping studies.

Pibrentasvir, co-formulated with glecaprevir is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Table 5.5.1: Identifiers, properties and naming of pibrentasvir

Property	Pibrentasvir
CAS Number	1353900-92-1
Chemical structure	
Molecular formula	$C_{57}H_{65}F_5N_{10}O_8$
Molecular weight	1113.2 g/mol
Chemical names	methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate.
ANN/INN	eBS ID: 111198 ANN and INN: Pibrentasvir

Scheduling status

Pibrentasvir is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

Pibrentasvir is approved in the USA as a prescription medicine.

Pibrentasvir is unclassified in New Zealand and Canada.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines;
- The new drug application; and

- Other.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.6 Voxilaprevir

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for voxilaprevir in the Poisons Standard as follows:

Schedule 4 – New Entry

VOXILAPREVIR.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- Voxilaprevir is a new chemical entity with no clinical/marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- Voxilaprevir in combination with sofosbuvir and velpatasvir (VOSEVI sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination tablet) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

c) the toxicity of a substance
- Reported adverse events from clinical trials include headache, fatigue, diarrhoea and nausea.

d) the dosage, formulation, labelling, packaging and presentation of a substance
- The fixed dose combination tablets voxilaprevir in combination with sofosbuvir and velpatasvir (VOSEVI) should be prescribed by medical professionals who are familiar with the management of viral hepatitis. The patients need to be instructed to follow the dosing regimens.

e) the potential for abuse of a substance
- Nil.

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

Scheduling proposal

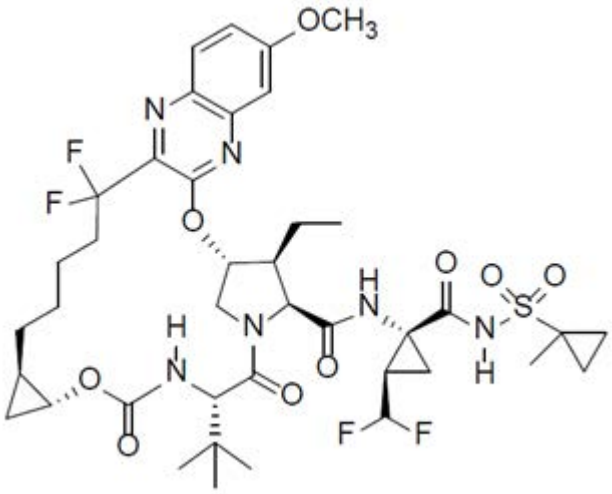
The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of voxilaprevir, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Voxilaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease. Voxilaprevir acts as a noncovalent, reversible inhibitor of the NS3/4A protease.

VOSEVI (sofosbuvir/velpatasvir/voxilaprevir fixed-dose combination) is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Table 5.6.1: Identifiers, properties and naming of voxilaprevir

Property	Voxilaprevir
CAS Number	1535212-07-7
Chemical structure	
Molecular formula	$C_{40}H_{52}F_4N_6O_9S$
Molecular weight	868.9 g/mol
Chemical names	(1*aR*,5*S*,8*S*,9*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-2-(difluoromethyl)-1-[(1-methylcyclopropanesulfonyl) carbamoyl] cyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1*a*,3,4,5,6,9,10,18,19,20,21, 22,22*a*-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide
ANN/INN	eBS ID: 111031 ANN and INN: Voxilaprevir

Scheduling status

Voxilaprevir is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

Voxilaprevir is unclassified in New Zealand, Canada and USA.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and

- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.7 Cerliponase alfa

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for cerliponase alfa in the Poisons Standard as follows:

Schedule 4 – New Entry

CERLIPONASE ALFA.

Implementation date: **1 June 2018**

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

a) the risks and benefits of the use of a substance
- Cerliponase alfa is a new chemical entity with no clinical/marketing experience in Australia.

b) the purposes for which a substance is to be used and the extent of use of a substance
- Cerliponase alfa is administered into the cerebral ventricles infusion via a surgically implanted intracerebroventricular (ICV) access device (reservoir and catheter).

c) the toxicity of a substance
- Cerliponase alfa is for intra thecal use.

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.

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of cerliponase alfa, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Cerliponase alfa is an enzyme replacement therapy. Cerliponase alfa is a recombinant pro-enzyme of human tripeptidyl peptidase-1 (rhTPP1, also known as BMN 190). It is administered into the cerebral ventricles infusion *via* a surgically implanted intracerebroventricular (ICV) access device (reservoir and catheter). The ICV access device must be surgically implanted prior to initiating cerliponase alfa infusions. Cerliponase alfa and the flushing solution, which is administered immediately following the cerliponase alfa to ensure a complete delivery, are both administered via ICV infusion. Cerliponase alfa must only be administered by a trained healthcare professional knowledgeable in ICV administration in a healthcare setting.

Brineura is indicated for the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Scheduling status

Cerliponase alfa is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

Cerliponase alfa is classified as a prescription medicine in the USA and the EU.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2018) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

5.8 Baricitinib

Delegate's final decision

Final decision:
The delegate has made a final decision to create a new Schedule 4 entry for baricitinib in the Poisons Standard as follows:

Schedule 4 – New Entry

BARICITINIB.

Implementation date: **1 June 2018**

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

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

- Baricitinib is a new chemical entity with no previous marketing experience in Australia.
- The risks and benefits of baricitinib have been considered and are outlined in the Product Information, Delegate's Request for ACM's Advice and TGA evaluation reports.

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

- Treatment should be initiated and monitored by a specialist medical practitioner with experience in the diagnosis and treatment of rheumatoid arthritis.
- Baricitinib has no previous experience of use in the community in Australia but is marketed in the European Union.
- It is proposed for use by patients in the community.
- Baricitinib is a JAK1/JAK2 inhibitor with weaker tyrosine kinase 2 inhibition.

c) the toxicity of a substance

- Baricitinib has risks that require medical intervention, monitoring, evaluation, diagnosis and treatment by a medical professional.

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

- The dosage is outlined in the Product Information for baricitinib. The labelling, packaging and presentation of baricitinib need to comply with the requirements for a prescription only medicine.

e) the potential for abuse of a substance

- Baricitinib does not appear to produce dependency and the potential for abuse is low.

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

- Nil.

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of baricitinib, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Baricitinib is an oral selective Janus kinase 1 (JAK1) and Janus kinase 2 (JAK2) inhibitor which function by inhibiting the activity of selective JAK1 and JAK2 enzymes, interfering with the JAK-STAT signalling pathway. This pathway is important in modulating the activity of inflammatory cytokines.

Baricitinib is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients. Baricitinib has been shown to improve physical function, reduce the signs and symptoms of RA. Baricitinib may be used as monotherapy or with conventional disease modifying anti-rheumatic drugs. Baricitinib should not be used with any other biological disease modifying anti-rheumatic drugs.

Scheduling status

Baricitinib is not specifically scheduled in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard that was in effect at the time the decision was made (Poisons Standard March 2018 (SUSMP No. 20)).

International regulations

Baricitinib is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2018) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.