Australian Government

Department of Health
Therapeutic Goods Administration

Publication of interim decisions proposing to amend, or not amend, the current Poisons Standard, February 2019

7 February 2019

Interim decisions have not been made for atranol and chlororatranol and for solvent yellow 33. The delegate is seeking further advice on how to most appropriately schedule skin sensitisers.

Publication of interim decisions made pursuant to regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (**the Regulations**)

In accordance with regulation 42ZCZP of the Regulations, this notice gives effect to the Secretary's obligation to publish the interim decisions, the reasons for those decisions and the proposed date of effect of decisions made pursuant to regulation 42ZCZN.

The interim decisions to which this notice relates include decisions made in respect to:

- proposed amendments referred to the November 2018 meeting of the Advisory Committee on Medicines Scheduling (ACMS #25);
- proposed amendments referred to the November 2018 meeting of the Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS #20); and
- proposed amendments referred to the November 2018 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #23).

Call for further submissions

In accordance with regulation 42ZCZP of the Regulations, this notice invites interested persons to make submissions to the Secretary in relation to the interim decisions on or before the close of business on **7 March 2019** (second closing date). See How to respond below.

How to respond

Your submission should:

- be relevant to the proposed amendment/s, including whether or not you support the amendment/s;
- address matters mentioned in section 52E of the *Therapeutic Goods Act 1989*;
- be submitted by the second closing date to medicines.scheduling@health.gov.au for substances referred to the ACMS or Joint ACMS-ACCS, or chemicals.scheduling@health.gov.au for substances referred to the ACCS. (Please include

'Proposed Amendments to the Poisons Standard (Medicines/Chemicals)' in the subject line of the email);

- ideally be no more than 3 pages; and
- be accompanied by a completed TGA Consultation submission coversheet.

Submissions might also include:

- Suggested improvements to the proposed amendments; and/or
- An assessment of how the proposed change will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.

Publication of submissions received on or before the second closing date

Pursuant to regulation 42ZCZQ(4) and (5), the Secretary will publish all public submissions received on or before the second closing date on the TGA's webpage titled: Public submissions on scheduling matters.

The Secretary will not, however, publish any information that the Secretary considers to be confidential information.

Accordingly, in order to assist the Secretary to make this assessment, please:

- complete a TGA Consultation submission coversheet (Microsoft Word, 65kb)
- highlight any text within the body of your submission that you want to remain confidential in grey and mark as 'IN CONFIDENCE'.

Further information about how TGA considers information which might be personal or sensitive in nature is set out below in the section titled Privacy and your personal information.

What will happen next

After considering all relevant submissions received on or before the second closing date (and or obtaining any further advice), the Secretary may make final decisions confirming, varying or setting aside the interim decisions. Final decisions will be published on the TGA's webpage titled Scheduling delegates' final decisions on **26 April 2019.**

Privacy and your personal information

The Therapeutic Goods Administration (TGA) collects your personal information in this submission in order to:

- Contact you if the TGA wants to seek clarification of issues raised in your submission or to check whether you consent to certain information that you have provided being made publicly available.
- Help provide context about your submission (e.g. to determine whether you are an individual or a director of a company or representing an interest group).

The TGA will disclose your name and (if applicable) your designation/work title on the TGA Internet site (i.e. make this information publicly available) if, when making your submission, you consent to the publication of your name on the TGA Internet site. 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 pubic submissions can be updated accordingly.

The TGA will not publish information it considers confidential, including yours/other individuals' personal information (unless you/they have consented to publication or it is required by law) 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.

Please do not include personal information about other individuals in the body of your submission. Personal information in this context means information or an opinion about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion.

For general privacy information, go to 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.

Enquiries

Any questions relating to submissions should be directed by email to medicines.scheduling@health.gov.au (for substances referred to the ACMS or Joint ACCS-ACMS) or chemicals.scheduling@health.gov.au (for substances referred to the ACCS).

Contents

Part A - Interim decisions on matters referred to an expert advisory committee (November 2018)

1. Advisory Committee on Medicines Scheduling (ACMS #25)

1.1 Nabiximols

Delegate's interim decision

Interim decision:

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

Reasons for the interim decision:

The reasons for the interim decision are as follows:

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

There is an emerging evidence base regarding the use of cannabinoids in multiple sclerosis (MS). Recent reviews consider the evidence for the use of cannabinoids for symptoms of MS and pain, and find modest effects (generally small effect sizes, and for pain, around 20 patients needing to receive cannabinoids for one to benefit). I note that in their pre-meeting public submission, Multiple Sclerosis Australia supported the down-scheduling proposal on the basis that decreased controls could result in potential cost saving to consumers.

However, while nabiximols has an established therapeutic value at therapeutic dosage levels, it is recognised to produce dependency and has a potential for misuse, abuse or illicit use. The risk of misuse and abuse of nabiximols preparations in the Australian context is difficult to accurately quantify on the basis of the current evidence, and therefore the loss of regulatory controls over prescribing for those with a drug dependency issue would seem premature.

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

Nabiximols are in an Australian approved product which is indicated as a treatment for symptom improvement in patients with moderate to severe spasticity due to MS, who have not responded adequately to other anti-spasticity medication, and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

Off-label use for other conditions has been explored, for example, for other pain conditions, and for the treatment of cannabis dependence. Patient exposure in Australia is still quite small with the applicant estimating 50 patients treated in 2017 and 100 patients in 2018.

c. the toxicity of a substance:

In clinical trials, adverse effects occur at a higher rate in the cannabinoid groups than in the placebo groups. Most effects are considered 'mild' to 'moderate'. In early clinical studies, 3/41 patients taking a high dose (18 sprays twice a day) in phase 1 studies experienced a toxic psychosis (which resolved spontaneously); 0/41 reported toxic psychosis at 12 sprays twice a day. Side effects also included cognitive impairment. However, nabiximols toxicity is not associated with a potential to cause serious outcomes such as sudden death.

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

Nabiximols as described in the current Schedule 8 entry are a highly characterised botanical

extract of defined chemotypes of *Cannabis sativa* L., containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the major constituents, together with other cannabinoid and non-cannabinoid components, and a range of other plant-based materials, such as terpenes, plant sterols, carotenoids and triglycerides. These are dissolved in a vehicle of ethanol and propylene glycol, with peppermint oil. The two principal cannabinoids, THC and CBD are present at concentrations of 27 mg/mL and 25 mg/mL respectively. The spray is administered via a metered dose pump giving a spray volume of 100 µL per spray. Hence each 100 µL spray is equivalent to 2.7 mg THC and 2.5 mg CBD. The dose required for effective relief is patient dependent and a titration regime is used to establish the individual dose.

e. the potential for abuse of a substance:

Nabiximols has THC as one of its major constituents. THC is the main psychoactive ingredient in cannabis and has known abuse potential and dependency.

The current Product Information for Sativex®, the Australian registered product with nabiximols as its active ingredient includes the following statement: "Sativex taken at the maximum recommended doses of up to 12 sprays per day has moderate potential for abuse. Patients with a history of substance abuse may abuse Sativex and if Sativex is being considered for these patients close monitoring is recommended".

A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of nabiximols in subjects with a history of recreational marijuana use found that abuse liability was broadly comparable to oral THC, particularly at higher doses within the therapeutic dose range[1].

The applicant indicates that their post-marketing data shows a low potential for illicit diversion and abuse of nabiximols after 82,000 patient years of exposure worldwide. Given that post-marketing reports are made voluntarily, this is not the most robust method for determining the abuse potential of a product.

THC has a well-established abuse liability when used outside therapeutic contexts, with around one in ten people who regularly use cannabis reported to develop dependence.

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

The UN Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (the UN Convention) refers to cannabis, cannabis plant (including cannabis leaves) and cannabis resin, extracts and tinctures. Under the Convention, extracts of cannabis are classified as Schedule I substances. According to the Scheduling Policy Framework 2018, any substance included in Schedule I or II of the UN Convention need to be classified in Schedule 8. Therefore, the inclusion of nabiximols in Schedule 8 is consistent with current scheduling policy. I also note from information provided by the applicant that in most other countries there are similar prescribing restrictions on nabiximols, and it is required to be stored in controlled drugs rooms.

Logistical issues with respect to refrigeration of S8 products are cited by the applicant as an impediment to distribution and wider use of their product. However, logistical issues are not a factor in scheduling (Scheduling Policy Framework 2018). Further, this is not an issue unique to nabiximols as there are other cannabis-based medicines that require cold chain storage and other Schedule 8 medicines are now being marketed that require refrigeration. Some jurisdictions already have legislative capacity to approve storage of Schedule 8 medicines other than in a standard drug safe, and others are working towards having this capacity due to the increasing number of refrigerated Schedule 8 products.

[1] Australian Public Assessment Report for Nabiximols, September 2013.

In their submission, the Australian Medical Association opposed the down-scheduling of nabiximols primarily due to the dosage form, noting also that they were not aware of the current scheduling arrangements impeding either appropriate prescribing of nabiximols or access by patients.

Noting that any other products containing THC are currently Schedule 8 it is not logical that products containing nabiximols should be considered not to be Schedule 8 also. There are now numerous different THC/CBD formulations and dose forms available in Australia with equivalent 1:1 ratios to nabiximols which are currently Schedule 8.

At some stage the listing for a specific ratio of THC:CBD may require review given not all cannabinoid products have comparable abuse liability, however the overall evidence is not yet available to be able to explicitly amend the scheduling of nabiximols. It would make sense that products with differing risk profiles could be potentially placed in different schedules, however there would need to be limits on the actual THC content of products.

Currently, the additional oversight around use of schedule 8 products appears appropriate with the limited clinical experience with nabiximols in Australia. With greater clinical experience to better understand the abuse and dependence liability in an Australian context, and if there were changes made to the UN convention that differentiated cannabinoids products based on their risk profile, product specific entries may be required to reflect the risk profile of different formulations.

Overall conclusions

On balance, I consider that the risk of misuse and abuse of nabiximols cannot be accurately quantified based of the current level of clinical evidence. In addition, amending the scheduling of nabiximols as proposed would be inconsistent with current scheduling policy and with the Schedule 8 status of other THC/CBD combinations for therapeutic use. Therefore, I consider that the loss of the current Schedule 8 regulatory controls over the prescribing of nabiximols would be premature, and I have therefore made the interim decision not to amend its current scheduling.

Materials considered

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

- The application to amend the current Poisons Standard with respect to nabiximols;
- The advice from the Advisory Committee on Medicines Scheduling (ACMS #25);
- The public submissions received before the first closing date;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal for nabiximols was published on the TGA website on 31 August 2018 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2018.

Background information for nabiximols

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to nabiximols. The application proposed to delete the Schedule 8 and Appendix D entries for nabiximols and create a new entry for nabiximols in Schedule 4.

Applicant's scheduling proposal and reasons

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

Schedule 4 – New Entry (modified version of current Schedule 8 entry)

NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where delta-9-tetrahydrocannabinol ~~tetrahydrocannabinols~~ and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray with a concentration of not more than 30 milligrams of cannabidiol per millilitre, and not more than 30 milligrams of tetrahydrocannabinols per millilitre, and registered on the Australian Register of Therapeutic Goods for human therapeutic use.

Schedule 8 – Delete Entry

~~# NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinols and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.~~

Appendix D, Item 1 – Delete Entry
~~NABIXIMOLS~~

Appendix K – Current Entry (No change proposed)
NABIXIMOLS

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NABIXIMOLS
cross reference: CANNABICHROMENE, CANNABIDIOL, CANNABIDIOLIC ACID, CANNABIDIVAROL, CANNABIGEROL, CANNABINOIDS, CANNABINOL, CANNABIS SATIVA, TETRAHYDROCANNABINOLIC ACID, TETRAHYDROCANNABINOLS, TETRAHYDROCANNABIVAROL

Schedule ~~8~~4
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The applicant's reasons for the proposal are:

- Nabiximols is regulated as an approved medicine and controlled under a Risk Management Plan in Australia by the TGA.
- Nabiximols at established therapeutic dosage levels does not produce dependency or have a high propensity for misuse, abuse, or illicit use.

- Nabiximols is currently available as a prescription medicine in 26 other countries with scheduling that is similar to Schedule 4 in Australia. This level of control has not led to abuse, diversion, dependence or use for illegal purposes of nabiximols.
- As of 26th June 2018 there have been no post-marketing reports of abuse or diversion reported spontaneously from healthcare professionals in the global safety database.
- Nabiximols meet the Scheduling Policy Framework criteria for Schedule 4.
- It is estimated that there have been 82060 patient years of exposure to nabiximols from post-marketing and compassionate use. There are no important interactions considered to be a safety concern, or emergent in the post-market data. The potential for interactions is managed in the current wording of the PI and monitored as part of the RMP and ASA through Pharmacovigilance.
- The risk profile of the nabiximols product is considered to be well defined.

Current scheduling status

Nabiximols is in Schedule 8 of the Poisons Standard as follows:

Schedule 8

NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinols and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.

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NABIXIMOLS
cross reference: CANNABICHROMENE, CANNABIDIOL, CANNABIDIOLIC ACID, CANNABIDIVAROL, CANNABIGEROL, CANNABINOIDS, CANNABINOL, CANNABIS SATIVA, TETRAHYDROCANNABINOLIC ACID, TETRAHYDROCANNABINOLS, TETRAHYDROCANNABIVAROL

Schedule 8
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Scheduling history

Scheduling of cannabinoids has been considered on several occasions over the last 30 years. Since 1984, nabilone, dronabinol (synthetic delta-9-tetrahydrocannabinol), cannabidiol and nabiximols have been listed in Schedules 8 or 4, to enable access for therapeutic use for specific medical conditions.

The scheduling of cannabis and its extracts has been considered by the National Drugs and Poisons Scheduling Committee (NDPSC) on a number of occasions. Currently, cannabis is a Schedule 9 substance, i.e., a prohibited substance which may be abused or misused and the

manufacture, possession, sale or use of which is prohibited by law. An exemption exists for cannabinoid substances listed in lower schedules, and for processed hemp fibre and its products containing 0.1 percent or less of tetrahydrocannabinol.

Dronabinol (delta-9-tetrahydrocanabinol) was considered by the NDPSC in 1994 following a recommendation that it be included in Schedule 8 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), for use in patients with advanced HIV disease with irreversible weight loss. At the time the NDSPC agreed to include dronabinol in Schedule 8 for therapeutic use.

Nabilone was considered at the July 1984 NDPSC meeting and included in Schedule 8 following that meeting. It is used as an anti-emetic in the treatment of nausea and vomiting caused by chemotherapy, primarily for patients who are not responsive to conventional anti-emetic treatments.

In February 2009, cannabidiol (CBD) was discussed by the National Drug and Poisons Scheduling Committee (NDPSC) as a part of a consideration of THC and the product [redacted] which led to the creation of the nabiximols entry (June and October 2009).

While the focus of the February 2009 meeting item was on the classification of THC, a number of public submissions received were regarding the availability of [redacted] which contains both THC and CBD. It was noted that it was difficult to give approval to special access scheme (SAS) applications for medications containing CBD as it was considered a Schedule 9 substance. However, access would be granted if CBD was placed in Schedule 8 for therapeutic use. This scheduling consideration was to be discussed at the June 2009 meeting.

In June 2009 the NDPSC considered scheduling requirements for the product [redacted], which contained CBD and small amounts of other cannabinoids, and its access under jurisdictional laws and the Special Access Scheme (SAS). Members agreed that it was appropriate to allow access to nabiximols and suggested that a pragmatic approach would be to create a Schedule 8 entry (listing the individual cannabinols and restricting its presentation to buccal sprays for therapeutic use) for this specific formulation, in conjunction with an Appendix D, paragraph 3 listing to facilitate its use within the various jurisdictions.

In October 2009, the NDPSC considered the scheduling of nabiximols after it was established that the United States of America Adopted Names Council had designated 'nabiximols' as the approved non-proprietary name for an extract of *Cannabis sativa.* This extract contained THC and CBD as major components and related cannabinoids and non-cannabinoid components alpha- and trans-caryophyllenes as minor components (i.e. the specific THC and CBD formulation considered appropriate for inclusion in Schedule 8 by the June 2009 meeting). The *Cannabis sativa* extract Schedule 8 entry was amended to nabiximols.

In May 2010, nabiximols was included in Schedule 8 and Appendices D and K. The Appendix D, Part 3 entry was made to limit access through the SAS. The Appendix K entry was agreed due to its sedating effects.

In March 2013, the committee advised that a change in the Appendix D entry for nabiximols from Paragraph 3 to Paragraph 1would be appropriate noting the requirement for specialist oversight for safe prescribing of the drug.

In November 2014, the ACMS considered the scheduling of cannabidiol. The committee recommended to the scheduling delegate that cannabidiol, including extracts of *Cannabis sativa*, and including preparations of up to 2% of cannabinoids, including cannabidivarin (CBDV) for therapeutic use, be included in Schedule 4. The reasons for the recommendation included:

- The condition that cannabidiol treats (the therapeutic use) requires diagnosis, management and monitoring under an appropriate medical practitioner.

- Cannabidiol has a safety profile which is consistent with a Schedule 4 listing.
- There is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties.

In May 2016, after extensive consultation, the scheduling delegate agreed with the committee recommendations and provided further reasons and clarification of the decision that included:

- The schedule entry needs to acknowledge that there is no pure form of cannabidiol currently available. However, low levels of impurities found in some cannabidiol products are not clinically significant and the scheduling entry should reflect this by allowing cannabinoids up to 2 %.
- The entry allows for, but does not specify, any particular non-active cannabis impurity/ies to be within the 'up to 2%'.
- The substances that comprise the 'up to 2%' must be substances found in cannabis. They cannot be synthetic cannabinoids.
- The entry does not preclude the cannabidiol and/or any other cannabinoids being derived from natural sources or made artificially, consistent with the interpretation of the schedules.
- Appendix D is not supported as the criteria are not met. It is considered that it is the medical condition for which CBD may be used which requires treatment by a specialist. Cannabidiol itself has no particular attributes that require it to be included in Appendix D. Scope of practice will ensure the appropriate prescribing of cannabidiol, rather than scheduling.

As a result, a Schedule 4 entry for cannabidiol was created, and the Schedule 9 entry for THC and their alkyl homologues was amended to exempt the new Schedule 4 entry for cannabidiol.

In November 2016, the Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS) further considered cannabidiol to improve the clarity of the entry with regards to the component cannabinoids found in cannabis. A final decision was made to improve the clarity of the cannabidiol entry on 31 May 2017, by including the word 'total' in relation to the other cannabinoids found in cannabis.

In March 2018, the ACMS provided advice to the delegate on a proposal to amend the Schedule 4 entry of cannabidiol, Schedule 8 entry of THCs and the Appendix K entries of cannabis and THCs to clarify the meaning of the cannabidiol Schedule 4 entry. On 7 June 2018 the delegate made an interim decision to amend the Schedule 4 entry for cannabidiol, and the Schedule 8 and Appendix K entries for tetrahydrocannabinols and cannabis in the Poisons Standard. A final decision on this proposal, has been published on the TGA web site on 28 September 2018, which

- Further clarifies that 'any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation';
- Clarifies the wording of the Schedule 8 entry references to cannabidiol in the tetrahydrocannabinols and cannabis entries; and
- Deletes references to hemp seed oil in the Schedule 8 entries for tetrahydrocannabinols and for cannabis because hemp seed oil is adequately controlled by the Schedule 9 entries for these substances.

In June 2018, the ACMS provided advice to the delegate on a further proposal to amend the Schedule entries for cannabidiol and tetrahydrocannabinols. An interim decision not to amend the Schedule entries for cannabidiol and tetrahydrocannabinols as proposed was published on 10 September 2018.

Australian regulations

There is one registered medicine currently active on the Australian Register of Therapeutic Goods (ARTG) that contains nabiximols ([redacted]) and one product containing cannabidiol which has been approved for export only.

According to the TGA Ingredient Database, cannabidiol is available for use as an active ingredient in Export Only and Prescription Medicines, and there is no reference to cannabis or THC.

In the last 30 years, in the Database of Adverse Events Notification (DAEN) - Medicines:

- There have been 2 reported cases of adverse events related to cannabidiol: 1 case with a single suspected medicine and no cases where death was a reported outcome;
- There have been 77 reported cases of adverse events related to cannabis: 77 cases with a single suspected medicine and 1 case where death was a reported outcome; and
- There have been no reported cases of adverse events related to THC.

International regulations

The following is an excerpt from the current application:

> *Nabiximols first obtained global marketing authorisation as a prescription medicine in the form of Sativex oromucosal (buccal) spray in 2005 (Canada). In 2010,* [redacted] *was first approved in the European Union (UK & Spain) and gained further approvals from numerous regulatory authorities including Germany and Italy. In the majority of these countries, the initial marketing authorisation was in legal categories equivalent to the Australian Schedule 4 - Prescription Only Medicine.*
>
> [redacted] *was first approved with conditions on 15th April 2005 in Canada. In the European Union (EU),* [redacted] *was approved in the United Kingdom and Spain via the decentralised procedure with the United Kingdom as the Reference Member State (RMS). Marketing Authorisations have also been granted through subsequent mutual recognition procedure (MRP) in Austria, Belgium, Czech Republic, Finland, Germany, Denmark, Sweden, Iceland, Italy, Luxembourg, Netherlands, Portugal, Slovakia, Norway, Poland, France and Ireland. In addition, in Europe, marketing authorisations have been granted for* [redacted] *in Switzerland and Liechtenstein. In the rest of the world, Marketing Authorisations have been granted in Israel, New Zealand, Australia, Brazil, Chile and Colombia.*

Substance summary

Nabiximols is a specific extract of *Cannabis sativa* which contains a range of cannabinoids, of which tetrahydrocannabinols and cannabidiol in approximately equal proportions comprise not less than 90% of the total cannabinoid content. Nabiximols are registered for use in Australia as a buccal spray preparation ([redacted]) as an adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults.

Nabiximols is comprised of two Botanical Drug Substances (BDS). These are:

- delta-9-tetrahydrocannabinol BDS (THC BDS)
- cannabidiol BDS (CBD BDS)).

The BDSs are whole extracts of *Cannabis sativa L.*

According to the approved Product Information document each mL Sativex oromucosal spray contains:

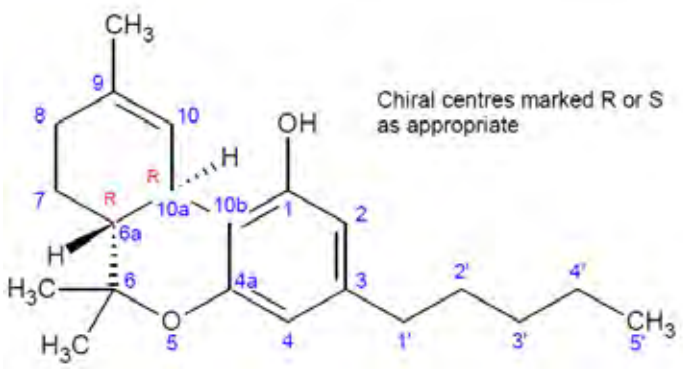
> 80 mg of extracts (nabiximols) from Cannabis sativa L., folium cum flore (Cannabis leaf and flower), corresponding to 27 mg delta-9-tetrahydrocannabinol (THC) and 25 mg cannabidiol (CBD) and lesser amounts of other cannabinoids (56 mg total cannabinoids).

Tetrahydrocannabinol

THC is one of at least 113 cannabinoids identified in cannabis and is the principal psychoactive constituent of cannabis.

The THC effects result from its partial agonist activity at the cannabinoid receptor CB1 located mainly in the central nervous system, and the CB2 receptor mainly expressed in cells of the immune system. The psychoactive effects of THC are primarily mediated by the activation of cannabinoid receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase.

Table 1: Chemical information

Property	Delta-9-tetrahydrocannabinol
Chemical structure	
Molecular formula	$C_{21}H_{30}O_2$
CAS numbers	1972-08-3
IUPAC and/or common and/or other names	(−)-(6aR,10aR)-6,6,9-trimethyl- 3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol; Dronabinol; Tetrahydrocannabinol; THC
Property	Delta-9-tetrahydrocannabinol
Chemical structure	(−)-(6aR,10aR)-6,6,9-trimethyl- 3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol; Dronabinol; Tetrahydrocannabinol; THC

Cannabidiol

Cannabidiol is a cannabinoid compound which occurs naturally in *Cannabis sativa* plants. The pharmacology of cannabidiol is complex and has been well characterised in *in vitro* environments.

Some cannabinoid compounds work by binding to the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) receptors in the brain. Cannabidiol does not activate CB1 and CB2 receptors directly. However, it has effects on many other 'signalling' systems and can be considered a 'multi-target' drug. Some of the effects of cannabidiol may be attributed to inhibition of the inactivation of endocannabinoids, such as anandamide. Other effects may be related to the chemical properties of the compound as opposed to pharmacodynamic effects. For example, it is thought that the presence of two hydroxyl groups enables cannabidiol to have an anti-oxidant action.

There is evidence that cannabidiol affects serotonin receptors (5HT1A), adenosine uptake, nuclear receptors of the peroxisome proliferator-activated receptors (PPAR) family and other pharmacological targets. The pharmacological targets of cannabidiol include receptors, ion channels, enzymes and cellular uptake processes.

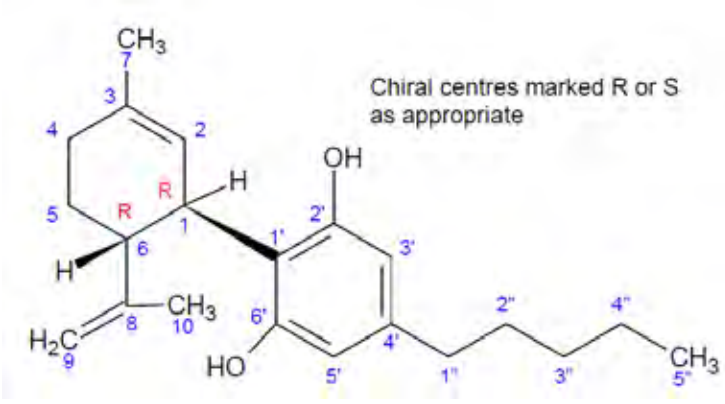
There are reports that cannabidiol possesses anti-proliferative, pro-apoptotic effects and inhibits cancer cell migration, adhesion and invasion. Evidence is also accumulating that there are positive effects of cannabidiol in the vasculature, where cannabidiol may induce vasorelaxation.

Information about the pharmacokinetics of the substance in humans is also accumulating. Oral absorption is slow and unpredictable relative to other routes of administration, possibly due to the chemical's poor water solubility. There is significant first pass metabolism where the concentration of ingested cannabidiol is greatly reduced before it is absorbed into systemic circulation, and the overall oral bioavailability may be as low as 6%. Other sources suggest an oral bioavailability of between 12 and 19%. Oromucosal and sublingual delivery, through sprays and lozenges, results in less variability with similar overall bioavailability.

The distribution of cannabidiol is governed by its high lipophilicity and there is rapid distribution to the brain, adipose tissue and other organs. It is also highly protein bound.

Like most cannabinoids, cannabidiol is extensively metabolised in the liver by cytochrome P450 enzymes, predominantly the CYP3A and CYP2C series. The terminal half-life is estimated to be 18-32 hours, although earlier work suggested a much shorter half-life of only 9 hours.

Table 1.2: Chemical information for Cannabidiol

Property	Cannabidiol
Chemical structure	
Molecular formula	$C_{21}H_{30}O_2$
CAS numbers	13956-29-1

Property	Cannabidiol
IUPAC and/or common and/or other names	2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (IUPAC)

Current use pattern in Australia

The only presentation of nabiximols currently available in Australia is [redacted] oromucosal spray, which is an ARTG-registered medicine for human use with the TGA approved indication:

> *"Treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy."*

Additional Therapeutic Indications Approved outside of Australia:

- For relief of neuropathic pain in patients with multiple sclerosis (MS).[2, 3, 4]
- For relief of persistent background pain in patients with cancer.[5, 6]

Nabiximols is currently approved and regulated in Australia under the brand name of [redacted] as an oromucosal spray containing 80 mg/mL nabiximols in a pump-actuated metered dose (AUST R 181978, CAS Number 1972-08-3).

Nabiximols is a botanical drug product developed for the treatment of spasticity in multiple sclerosis. According to the AusPAR for nabiximols[7], the active ingredient is a highly characterised botanical extract of defined chemotypes of *Cannabis sativa* L., containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the major constituents, together with other cannabinoid and non-cannabinoid components. These are dissolved in a vehicle of ethanol and propylene glycol, with peppermint oil. The two principal cannabinoids, THC and CBD are present at concentrations of 27 mg/mL and 25 mg/mL respectively. In addition to these two main cannabinoids, nabiximols also contains a range of minor cannabinoids and plant-based materials, such as terpenes, plant sterols, carotenoids and triglycerides. The spray is administered via a metered dose pump giving a spray volume of 100 µL per spray. Hence each 100 µL spray is equivalent to 2.7 mg THC and 2.5 mg CBD. The dose required for effective relief is patient dependent and a titration regime is used to establish the individual dose. The cannabis plants are propagated through cuttings and are grown under managed indoor conditions in glasshouses to assure their genetic reproducibility and consistent quality of the extracts.

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[2] Rog D J N, T J, Friede T, Young C A. (2005). Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* ;**65:**812-819.

[3] Barnes MP. (2006) [redacted]: Clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin. Pharmacother.***7(5):**607-615.

[4] Rog DJ, Nurmikko TJ, Young CA. (2007). Oromucosal delta-9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin. Ther.*;**29(9):**2068-2079.

[5] Johnson JR, Wright S. (2005). Cannabis-based medicines in the treatment of cancer pain: a randomised, double-blind parallel group, placebo-controlled, comparative study of the efficacy, safety and tolerability of [redacted] and tetranabinex in patients with cancer related pain. *J. Support. Oncol.*;**3(5.Supplement 3):**21

[6] Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT (2012). Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain.* **13(5):**438-49.

[7] Australian Public Assessment Report for Nabiximols, September 2013.

As part of the human endocannabinoid system (ECS), cannabinoid (CB) receptors, CB1 and CB2 receptors are found predominantly at nerve terminals where they have a role in retrograde regulation of synaptic function. THC acts as a partial agonist at both CB1 and CB2 receptors, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g. reduce effects of excitatory neurotransmitters such as glutamate).

In animal models of MS and spasticity CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. These effects are prevented by CB antagonists, and CB1 knockout mice show more severe spasticity. In the chronic relapsing experimental autoimmune encephalomyelitis mouse model, nabiximols produced a dose-related reduction in the hind limb stiffness.

Pharmacodynamic properties

Anatomical Therapeutic Chemical (ATC) Code: NO2BG10

The endocannabinoid system comprises of cannabinoid receptors, endogenous cannabinoids (endocannabinoids) and their synthetic and degradative enzymes. There have been two cannabinoid (CB) receptors (CB1 and CB2) isolated and cloned to date, both are members of the super-family of G-protein coupled receptors.[8] In addition to these established CB receptors, there are several proposed novel cannabinoid receptors including (but not limited to) the endothelial anandamide receptor and GRP55.[9] CB1 receptors are highly expressed in neuronal tissue, where they predominantly inhibit neurotransmitter release at nerve terminals. CB1 receptors are also expressed in non-neuronal tissues such as the liver and adipose tissue, as well as the cardiovascular, urinary and reproductive systems.[10] In contrast, CB2 receptors are expressed mainly by immune tissues, such as the spleen and thymus as well as in circulating/resident immune cells. However, recent publications have indicated that CB2 receptors are functionally active in brain neurons and pain pathways.[8, 11] The endocannabinoid system is thought to act as a fine-tuning system regulating and maintaining body homeostasis.

The first endocannabinoids identified were N-arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG).[12] These transmitters are not stored and released like classical neurotransmitters, but are synthesised on demand in response to elevations of intracellular calcium. Once released, the endocannabinoid activates CB receptors and the biological actions are then terminated by cellular reuptake via the putative endocannabinoid transporter.[12] Termination of endocannabinoid signalling is initiated by two hydrolytic enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). FAAH predominantly degrades anandamide into fatty acids and ethanolamine, whereas MAGL is thought to be the major 2-AG degrading enzyme.[12]

THC binds to the CB1 and CB2 receptors with nanomolar affinity and acts as a partial agonist13. In contrast, CBD binds to CB1 and CB2 receptors with micromolar affinity and does not appear

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[8] Pertwee, R.G., et al. (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB1 and CB2. *Pharmacological Reviews*, **62(4):** 588-631.
[9] Atwood, B.K. and Mackie, K. (2010). CB2: a cannabinoid receptor with an identity crisis. *Br J Pharmacol*, **160(3):** 467-79.
[10] Di Marzo, V. (2009). The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation. *Pharmacol Res*. **60(2):** 77-84.
[11] Van Sickle, M.D., et al. (2005). Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*. **310 (5746):** 329-32.
[12] De Petrocellis, L., M.G. Cascio, and Di Marzo, V. (2004). The endocannabinoid system: a general view and latest additions. *Br J Pharmacol*. **141(5):** 765-74.

to activate CB receptors.[13] However, the effects of CBD can be antagonised by pharmacological blockade of the CB1 or CB2 receptors; this may be due to inhibitory actions of CBD at very high doses at FAAH, which would act to increase local anandamide levels which may then indirectly activate CB receptors.[14, 15] In addition to activating CB receptors which are negatively coupled to adenylate cyclase (GI) and positively coupled to mitogen activated protein, THC and CBD can act on other biological targets, these include allosteric modulation of receptors for serotonin, glutamate and noradrenaline, modulation of various ion channels, enzymes and neurotransmitter transporters.[8,15]

The principal pharmacological actions of THC include analgesia, anti-inflammatory actions, neuroprotection, reduced GI motility and secretion, tachycardia and hypotension, reduced intra-ocular pressure, relief from muscle spasm, anti-emetic properties, appetite stimulation and psychoactive effects such as elevation of mood, altered perception and cognition.[15] CBD has similar properties where analgesia, anti-inflammatory actions, neuroprotective and antiemetic properties are observed. In addition to these actions, CBD is also reported to act as an anxiolytic drug and possess anticonvulsant properties.[15] An important difference between the pharmacological properties of CBD and THC is that CBD lacks the central psychoactive effects of THC. When CBD is co-administered with THC, it can both enhance and reduce the effects of THC depending on the experimental or clinical conditions.[15]

Pharmacokinetic properties

Absorption

There is a high degree of variability between patients in pharmacokinetic parameters.

Distribution

Following a single oromucosal administration, maximum plasma concentrations of both CBD and THC typically occur within two hours. When [redacted] is administered oromucosally, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose. A dose of 6.65 mg of vaporised THC extract, administered by inhalation resulted in mean plasma C_{max} of more than 100 ng/mL within minutes of administration, with significant psychoactivity. With [redacted], a mean C_{max} of about 4 ng/mL was reached some 45-120 minutes after a single dose administration of 10.8 mg (THC) dose, and was generally well tolerated with little evidence of significant psychoactivity.[16] The resultant concentrations in the blood are lower than those obtained by inhaling the same dose because absorption is slower and redistribution into fatty tissues is rapid. Additionally, some of the THC undergoes hepatic first pass metabolism to 11-OHTHC, the first metabolite of THC, which then undergoes further oxidation to 11-nor-9-COOH-THC, the most abundant metabolite of THC.

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[13] Pertwee, R.G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *British journal of Pharmacology*. **153(2):** 199-215.

[14] De Petrocellis, L., et al. (2004). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*, **163:** 1479-94.

[15] Pertwee, R.G. (2004). Pharmacological and therapeutic targets for delta tetrahydrocannabinol and cannabidiol. *Euphytica* **140(1):** 73-82.

[16] Etges, T., et al. (2016). An observational post marketing safety registry of patients in the UK, Germany, and Switzerland who have been prescribed [redacted] (THC:CBD, Nabiximols) oromucosal spray. *Therapeutics and Clinical Risk Management*. **12:** 1667-1675.

Table 1.3: Pharmacokinetic parameters for [redacted], for vaporised THC extract and smoked cannabis

	Cmax THC ng/mL	Tmax THC minutes	AUC (0-t) THC ng/mL/min
[redacted] (providing 21.6 mg THC)	5.40	60	1362
Inhaled vaporised THC extract (providing 8 mg THC)	118.6	17.0	5987.9
Smoked cannabis[13] (providing 33.8 mg THC)	162.2	9.0	No data

Metabolism

THC and CBD are metabolised in the liver. Human hepatic cytochrome P450-2C9 isozyme catalyses the formation of 11-OH-THC, the primary metabolite, which is further metabolised by the liver to other compounds including 11-nor-carboxy-delta-9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The cytochrome P450-3A sub-family catalyse the formation of other hydroxylated minor metabolites. CBD is extensively metabolised and more than 33 metabolites have been identified in urine. The major metabolic route was hydroxylation and oxidation at C-7 followed by further hydroxylation in the pentyl and propenyl groups. The major oxidized metabolite identified was CBD-7-oic acid containing a hydroxyethyl side chain.

Protein binding of THC is high (~97%). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream, then metabolised and excreted via the urine and faeces.

Elimination

From clinical studies with [redacted], a non-compartmental PK analysis shows that the first order terminal elimination half-life from plasma is 1.94, 3.72 and 5.25 hours for THC and 5.28, 6.39 and 9.36 for CBD following the administration of 2, 4 and 8 sprays respectively. From the literature, elimination of oral cannabinoids from plasma is bi-phasic with an initial half-life of approximately four hours, and the terminal elimination half-lives are of the order of 24 to 36 hours or longer. Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

Pre-clinical safety data

The following information is taken from the Australian approved Product Information for Sativex.

Effects in nonclinical toxicity and safety pharmacology studies were observed only at exposures sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Sativex or a mixture of its component extracts was not genotoxic in *in vitro* tests for bacterial reverse mutation and *in vivo* micronucleus tests for clastogenicity in mice and rats, or in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes. No consistent genotoxicity was seen in an *in vitro* test for forward mutation in mouse L5178Y cells.

Fertility in rats was unaffected by oral treatment with a 1:1 mixture of THC BDS and CBD BDS, at doses up to 12.5 mg/kg/day or each active component. This dose resulted in estimated exposures that were well in excess of that expected in humans with the maximum recommended dose (>300 fold based on AUC). Effects on various male reproductive parameters have been reported with cannabinoids in some animal studies, but findings were inconsistent or observed at high/toxic doses and their clinical significance is uncertain.

There was no evidence for teratogenicity in rats and rabbits treated with oral doses of a 1:1 THC BDS and CBD BDS mixture of up to 12.5 mg/kg/day of each active component. This dose resulted in respective THC and BDS exposures (based on AUC) that were approximately 490 and 320 fold (rats) or 12.5 and 3 fold (rabbits) those expected in humans with the maximum recommended dose. The highest dose was maternotoxic in rabbits and resulted in a slightly lower fetal weight and impaired skeletal ossification. Reduced fetal weights and increased incidences of skeletal variants were seen in rabbits, associated with maternal toxicity which was apparent with all doses tested.

Oral treatment of rats with 4 mg/kg/day of a 1:1 THC BDS and CBD BDS mixture from the time of implantation to weaning of the offspring resulted in a lower pup body weight gain and slightly impaired righting reflex on day 5 of lactation. The NOEL for these findings (2 mg/kg/day) was below the maximum recommended human dose in terms of body surface area.

In studies with animals, as expected, due to the lipophilic nature of cannabinoids, considerable levels of cannabinoids were found in the maternal breast milk. Following repeat dosing, cannabinoids are concentrated in breast milk (40 to 60 times the plasma level). Doses in excess of normal clinical doses may affect growth rates of breast-fed infants.

Pre-meeting public submissions

Six public submissions were received before the first closing date in response to an invitation published on 31 August 2018 under regulation 42ZCZK of the Regulations. Three of the submissions were in support of the proposal while three were opposed.

The main points in support of the applicant's proposal:

- Nabiximols meet the Scheduling Policy Framework and the criteria under Section 52(e) for inclusion in Schedule 4 on the basis of its overall safety profile and characteristics including low potential for physical or psychological dependence, misuse and abuse.
- Intoxication effects following use of nabiximols are reported to be low so dependence on nabiximols is suggested to be unlikely.
- The characteristics of nabiximols with respect to the potential for abuse meet the scheduling factor for Schedule 4 ('The use of the substance at therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use.')
- Adverse effects most commonly reported are mild or moderate dizziness, fatigue or fainting, which are most frequent in the first few weeks of therapy and resolve without discontinuation.
- Nabiximols is not widely used and is only approved for use by a subset of a particular patient population. As the product is not listed on the Pharmaceutical Benefits Scheme it would only be accessed by patients with multiple sclerosis willing to pay privately.
- Patient factors would be assessed by the relevant prescriber when considering initiation of treatment with nabiximols, and responses to treatment can be managed through monitoring of patients, particularly with regards to adverse effects of initial doses.

- The down scheduling of nabiximols and deletion of the Appendix D entry will make the prescribing, storing, transporting and distribution of nabiximols easier, resulting in potential cost savings for consumers particularly as nabiximols is not currently listed on the PBS.
- The storage requirements for nabiximols as a Schedule 8 medicine are challenging for pharmacists.
- The particular formulation of this product requires refrigeration which is difficult as most jurisdictions require Schedule 8 medicines to be stored in a Controlled Drugs safe. In NSW new storage requirements for Schedule 8 medicines that require refrigeration for community pharmacies, pharmacies in a public hospital, or pharmacies in a private hospital. This presents challenges at present for pharmacists in meeting storage requirements for Schedule 8 medicines. For a product such as [redacted] that meets all the scheduling factors for Schedule 4, it would appear unnecessary to make an exemption for refrigerated Schedule 8s when these products are more suited to Schedule 4.
- Nabiximols has made a valuable addition to the repertoire of medications available to people with MS and their healthcare teams. It allows for an appropriate treatment choice to be made according to the efficacy and possible side-effects in relation to an individual's circumstances and, with these further amendments to scheduling, has the potential to help alleviate the economic cost of MS to individuals, their families and the broader community.
- Easy-to-use medications for MS such as [redacted] are of great benefit for people living with MS in rural and regional settings where the need for hospital and clinic visits can be minimised or not needed at all.

The main points against the applicant's scheduling proposal include:

- The proposed scheduling change is inconsistent with the current scheduling requirements for cannabis and tetrahydrocannabinols.
- No evidence was provided that the specific properties of the [redacted] formulation confer a degree of safety distinct from any other formulation containing both CBD and THC.
- The proposal is aimed at a particular product, while the Poisons Standard considers the scheduling of 'substances'.
- It is timely for the committee to consider whether there is a need for a separate scheduling entry for nabiximols in the Poisons Standard.
- There is potential for harm, including serious adverse effects, from
  - known interactions (induction or inhibition of drug metabolising enzymes, additive CNS depressant effects with sedatives, hypnotics and alcohol) and
  - potentially from others not previously elucidated
  - Additive muscle relaxant effects and subsequent falls risk.
- As nabiximols contains the psychoactive cannabinoid THC, there is potential for misuse, abuse, illegal use or diversion, particularly in light of the illicit market for street cannabis. The applicant's assertion of a lack of spontaneous reporting of such is not indicative of its absence.
- Down-scheduling would potentially lead to prescribing by practitioners with limited knowledge of appropriate indications, contraindications and drug interactions, and may lead to patient pressure on practitioners to prescribe.

- The delivery mechanism - a spray – has a similar effect to giving the medicine intravenously. This is an important contraindication for its down-scheduling to a less controlled category of medicine.
- Further research is needed investigating incidence of cannabis dependency with supra-therapeutic use.
- Down-scheduling of nabiximols would reduce the potential for monitoring adverse effects.
- The AMA is not aware of any difficulties experienced by medical practitioners who wish to appropriately prescribe this medicine to their patients under the current scheduling arrangements, nor of patients having difficulty in accessing the medicine appropriately.
- It would introduce inconsistency within the Poisons Standard given that the NABIXIMOLS entry provides for the spray (dose form is explicit in the entry) to contain no more than 30mg of tetrahydrocannabinols per millilitre, together with approximately equal proportions of cannabidiol. This would place the entry in conflict with the listings for CANNABIDIOL.
- The claim by the applicant that the scheduling of nabiximols in 26 other countries is similar to Schedule 4 in Australia is questionable.
- There are unique regulatory structures underlying the scheduling of cannabis in other countries and there is also a paucity of longitudinal outcome data related to potential for abuse, diversion, dependence or use for illegal purposes.
- There are inherent limitations of post-marketing reporting in the global safety database, as this is reliant upon spontaneous reporting. Reliance upon data derived via spontaneous reporting is likely to underreport any potential public health risk signals.

Joint ACMS-ACCS advice

The committee recommended that the current scheduling of nabiximols remains appropriate and no changes to the Poison Standard were proposed.

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

The reasons for the advice included:

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

- There is an emerging evidence base regarding the use of cannabinoids in multiple sclerosis.
- Recent reviews consider the evidence for the use of cannabinoids for symptoms of multiple sclerosis and pain, and find modest effects (generally small effect sizes, and for pain, around 20 patients needing to receive cannabinoids for one to benefit).

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

- [redacted] is indicated as a treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

- Off-label use for other conditions have been explored (e.g. other pain conditions, and for the treatment of cannabis dependence).
- Nabiximols has therapeutic use and therefore Schedule 8 is applicable, rather than Schedule 9.

(c) the toxicity of a substance:

- In clinical trials, adverse effects occur at a higher rate in the cannabinoid groups than placebo groups.
- Most adverse effects are considered 'mild' to 'moderate'.
- In early clinical studies, 3/41 patients taking a high dose (18 sprays twice a day) in phase 1 studies experienced a toxic psychosis (resolved spontaneously), 0/41 reported toxic psychosis at 12 sprays twice a day. Side effects also include cognitive impairment.

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

- Nabiximols is a highly characterised botanical extract of defined chemotypes of *Cannabis sativa* L., containing delta-9- tetrahydrocannabinol (THC) and cannabidiol (CBD) as the major constituents, together with other cannabinoid and non-cannabinoid components. These are dissolved in a vehicle of ethanol and propylene glycol, with peppermint oil. The two principal cannabinoids, THC and CBD are present at concentrations of 27 mg/mL and 25 mg/mL respectively. In addition to these two main cannabinoids, [redacted] also contains a range of minor cannabinoids and plant-based materials, such as terpenes, plant sterols, carotenoids and triglycerides.
- The spray is administered via a metered dose pump giving a spray volume of 100 µL per spray. Hence each 100 µL spray is equivalent to 2.7 mg THC and 2.5 mg CBD.
- The dose required for effective relief is patient dependent and a titration regime is used to establish the individual dose.
- The cannabis plants are propagated through cuttings and are grown under managed indoor conditions in glasshouses to assure their genetic reproducibility and consistent quality of the extracts.

(e) the potential for abuse of a substance

- A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of [redacted] in subjects with a history of recreational marijuana use found that abuse liability was broadly comparable to oral THC, particularly at higher doses within the therapeutic dose range.
- Well-conducted research indicates that oral THC has a lower abuse liability that smoked THC.
- THC has a well-established abuse liability when used outside therapeutic contexts. Around one in ten people using cannabis regularly are reported to develop dependence.
- Evidence is currently limited, but indicates there is potential for misuse and abuse.

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

- This listing for a specific ratio of THC:CBD may require review – to date, little evidence has explored differing ratios. It is likely that as studies that explore differing ratios emerge, and the role of cannabidiol in different clinical conditions becomes clearer, that we will start to see products with a range of ratios.

- Other THC/CBD combination preparations are included in Schedule 8. Nabiximols could be described as an extract of cannabis. Extracts of cannabis are in Schedule I of the UN Single Convention on Narcotic Drugs. The Scheduling Factors for Schedule 8 require Schedule I and II substances to be included in Schedule 8.
- States and territories have enacted mechanisms to allow convenient storage of S8 refrigerated products.

1.2 Racetams

Delegate's interim decision

Interim decision:

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

Schedule 4 – New Entries

RACETAMS

except when separately specified in these Schedules.

ANIRACETAM.

COLURACETAM.

DIMIRACETAM.

FASORACETAM.

METHYLPHENYLPIRACETAM.

NEBRACETAM.

NEFIRACETAM.

OMBERACETAM.

OXIRACETAM.

PHENYLPIRACETAM.

PRAMIRACETAM.

ROLZIRACETAM.

SELETRACETAM.

SUNIFIRAM.

UNIFIRAM.

Appendix K – New entry

SELETRACETAM

Index – New Entries

RACETAMS

Schedule 4

ANIRACETAM
cross reference: RACETAMS

Schedule 4

COLURACETAM
cross reference: RACETAMs

Schedule 4

DIMIRACETAM
cross reference: RACETAMS

Schedule 4

FASORACETAM
cross reference: RACETAMS

Schedule 4

METHYLPHENYLPIRACETAM
cross reference: RACETAMS

Schedule 4

NEBRACETAM
cross reference: RACETAMS

Schedule 4

NEFIRACETAM
cross reference: RACETAMS

Schedule 4

OMBERACETAM
cross reference: RACETAMS

Schedule 4

OXIRACETAM
cross reference: RACETAMS

Schedule 4

PHENYLPIRACETAM
cross reference: RACETAMS

Schedule 4

PRAMIRACETAM
cross reference: RACETAMS

Schedule 4

ROLZIRACETAM
cross reference: RACETAMS

Schedule 4

SELETRACETAM
cross reference RACETAMS

Schedule 4

Appendix K

Schedule 4

SUNIFIRAM
cross reference: RACETAMS

Schedule 4

UNIFIRAM
cross reference: RACETAMS

Index – Amended Entries

BRIVARACETAM
cross reference: RACETAMS

Schedule 4

Appendix K

LEVETIRACETAM
cross reference: RACETAMS

Schedule 4

Appendix K

PIRACETAM
cross reference: RACETAMS

Schedule 4

Proposed date of effect of the proposed amendment: **1 June 2019**

Reasons for interim decision:

The reasons for the interim decision are as follows:

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

There is worldwide interest in racetams for the treatment of CNS disorders including epilepsy, dementia, stroke, ischaemia and stress. They are also used in efforts to restore memory and brain performance in encephalopathies including cranial traumas and inflammation. Those that remain in development and clinical use seem to be well tolerated with low potential for drug interactions. With an increasing ageing population and incidence of degenerative disorders (dementias) clinical trials with this group of substances and their derivatives are likely to continue. This clinical use justifies prescription medicine status.

Racetams can be purchased over the internet and are claimed to be memory enhancers based on animal studies. These substances can cause a range of adverse effects, including psychomotor excitability, insomnia, heartburn, stomach pain, dysphoria, tiredness, dizziness, memory loss, headache and severe diarrhoea. The long term effects are largely unknown, but in animal studies nefiracetam caused renal and testicular toxicity, aniracetam was a reproductive toxin. There is a risk that these substances are being used by healthy individuals, with consequent potential acute and long term harm.

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

Racetams are used clinically for treatment of CNS disorders including epilepsy, dementia, stroke, ischaemia and stress. They are also used in efforts to restore memory and brain performance in

encephalopathies including cranial traumas and inflammation.

Other than brivaracetam, levetiracetam and piracetam, none of the racetams are in any products on the ARTG, but can be purchased over the internet.

c. the toxicity of a substance:

The toxicity of these 15 racetams is poorly studied, but some cause psychomotor agitation, dysphoria, insomnia, heartburn, stomach pain, which are likely to occur with all 'cognitive enhancers'.

For those racetams still currently available in clinical use, toxicity is considered low, while those that are no longer in clinical use have greater toxicity. The long term effects from use of these racetams are not known, but reproductive, testicular, gastrointestinal and renal toxicity have been seen in animals.

Brivaracetam and levetiracetam are listed in Appendix K (sedation warning). Seletracetam is also likely to cause sedation as it is similar to brivaracetam and levetiracetam, and somnolence was reported as a common adverse event in clinical in trials.

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

No products containing these 15 racetams (aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram) are approved therapeutic substances in Australia and are not in any therapeutic goods on the Australian Register of Therapeutic Goods.

e. the potential for abuse of a substance:

While there is no clear evidence for dependence or abuse, these substances are being used without evidence of efficacy. Despite the claims that the substances are memory enhancers (based on animal studies only) there are reports of consumers obtaining racetams online as 'smart drugs' for cognition enhancement or supplements for memory performance.

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

Nil.

Overall conclusions

On balance, I consider that the risks of adverse events from racetams outweigh the potential benefits of them remaining available without any restrictions. There is inadequate information on their potential to cause adverse events with short or long-term use, and evidence of significant potential harms based on animal studies. I have therefore made the interim decision that these substances should be prescription-only medicines.

While the individual substances are captured by the current Schedule 4 entries for the racetams brivaracetam, levetiracetam and piracetam as 'derivatives' of these substances, by making specific entries for each substance their Schedule 4 status will be clarified. The group entry for racetams will also capture any additional racetams not specifically mentioned in an individual Poisons Standard entry.

Additionally, in light of the existing Appendix K entries for brivaracetam and levetiracetam (sedation warning), I have also decided to create an Appendix K entry for seletracetam which like brivaracetam and levetiracetam, has anti-convulsant activity.

Materials considered

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

- The proposal to amend the current Poisons Standard with respect to racetams;
- The advice received from the Advisory Committees on Medicines Scheduling (ACMS #25);
- The public submissions received before the first closing date;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal for racetams was published on the TGA website on 31 August 2018 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2018.

Background information for racetams

Delegate's referral to ACCS/ACMS

The proposed amendments to the Poisons Standard are to creating a new Schedule 4 group entry for racetams and new specific Schedule 4 entries for aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram.

Delegate's scheduling proposal and reasons

This is a delegate initiated application. The delegate's proposed amendments to the Poison Standard are:

Schedule 4 – New Entry

RACETAMS

except when separately specified in these Schedules.

ANIRACETAM.

COLURACETAM.

DIMIRACETAM.

FASORACETAM.

METHYLPHENYLPIRACETAM.

NEBRACETAM.

NEFIRACETAM.

OMBERACETAM.

OXIRACETAM.

PHENYLPIRACETAM.

PRAMIRACETAM.

ROLZIRACETAM.

SELETRACETAM.

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UNIFIRAM.

Appendix K – New entry

SELETRACETAM

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SUNIFIRAM
cross reference: RACETAMS

Schedule 4

UNIFIRAM
cross reference: RACETAMS

The reasons for the proposal are:

- Aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram are not specifically scheduled. Although captured as derivatives by the Schedule 4 entries for the racetams, brivaracetam, levetiracetam and piracetam, specifically scheduling these racetams will clarify their scheduling status as Schedule 4 substances.
- Due to their potential use and adverse events, the proposal recommends that these should be prescription only medicines.

Current scheduling status

The racetams brivaracetam, levetiracetam and piracetam are currently in Schedule 4 (Prescription Only Medicine) of the Poison Standard as follows:

Schedule 4

BRIVARACETAM.

LEVETIRACETAM.

PIRACETAM.

Brivaracetam and levetiracetam are also in Appendix K (*Drugs required to be labelled with a sedation warning*) as follows:

Appendix K

BRIVARACETAM

LEVETIRACETAM

Aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram are not specifically scheduled but are all captured as derivatives of the Schedule 4 entries for brivaracetam, levetiracetam and piracetam as above.

Scheduling history

Aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram have not been previously considered for scheduling.

Brivaracetam

In November 2016 the Advisory Committee on Medicines Scheduling (ACMS) considered and recommended the creation of new entries for brivaracetam in Schedule 4 and Appendix K of the Poisons Standard. Based on the indication, risks and benefits of brivaracetam (among other considerations), the delegate agreed and published a final decision on the TGA website on 23 March 2017, with a 1 June 2017 implementation date.

Levetiracetam

In May 2001 the National Drugs and Poisons Schedule Committee (NDPSC) considered scheduling the new chemical entity, levetiracetam. Noting the pharmacodynamic characteristics of levetiracetam, the indication, and that the treatment of epilepsy requires ongoing medical supervision and management, the committee decided that Schedule 4 was appropriate for levetiracetam. The committee also agreed that given the very common side effect of somnolence (>10%), an Appendix K entry was appropriate.

Piracetam

In October 2006, the NDPSC decided to harmonise with New Zealand the make piracetam a Schedule 4 substance. It was noted that there were no products containing piracetam on the Australian Register of Therapeutic Goods (ARTG) at that time.

Australian regulatory history

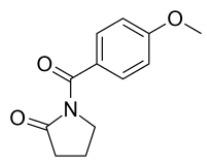
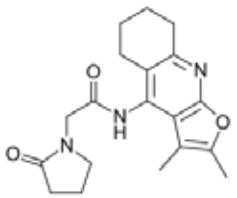
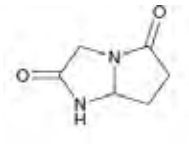
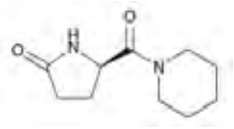
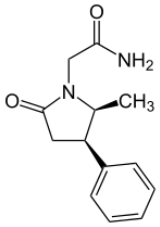
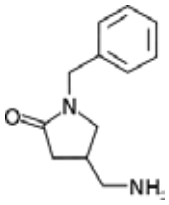
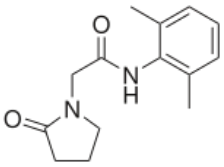
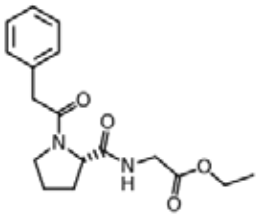
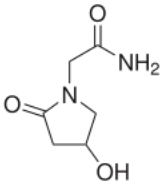
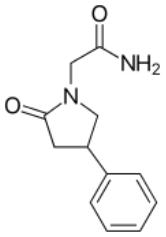
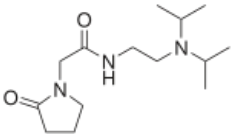
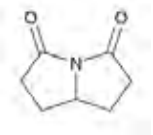
None of the 15 racetams (aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram) are permitted for use in listed medicines in Australia according to the Therapeutic Goods (Permissible Ingredients) Determination No.3 of 2018.

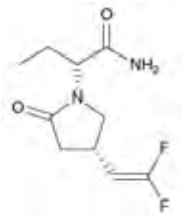
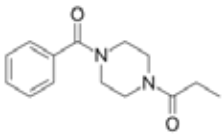
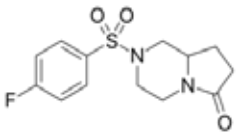
None of the 15 racetams (aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram) are approved therapeutic substances in Australia and are not in any therapeutic goods on the Australian Register of Therapeutic Goods.

Substance summary

There is increasing interest in racetam nootropic drugs for the treatment of Central Nervous System (CNS) disorders including epilepsy, neurodegenerative diseases such as dementia and Alzheimer's disease, stroke, ischemia and stress. These agents are also used in efforts to restore memory and brain performance in patients with encephalopathies of various aetiologies, including cranial traumas and inflammation.

Figure 1: Nootropic drugs of the racetam family and piracetam-like substances sunifiram and unifiram

			
Aniracetam 72432-10-1 $C_{12}H_{13}NO_3$ 219.24 g/mol	**Coluracetam** 135463-81-9 $C_{19}H_{23}N_3O_3$ 341.411 g/mol	**Dimiracetam** 126100-97-8 $C_6H_8N_2O_2$ 140.142 g/mol	**Fasoracetam** 110958-19-5 $C_{10}H_{16}N_2O_3$ 196.25 g/mol
			
Methylphenylpiracetam $C_{13}H_{16}N_2O_2$ 232.28 g/mol	**Nebracetam** 97205-34-0 $C_{12}H_{16}N_2O$ 204.273 g/mol	**Nefiracetam** 77191-36-7 $C_{14}H_{18}N_2O_2$ 246.31 g/mol	**Omberacetam** 157115-85-0 $C_{17}H_{22}N_2O_4$ 318.373 g/mol
			
Oxiracetam 62613-82-5 $C_6H_{10}N_2O_3$ 158.157 g/mol	**Phenylpiracetam** 77472-70-9 $C_{12}H_{14}N_2O_2$ 218.256 g/mol	**Pramiracetam** 68497-62-1 $C_{14}H_{27}N_3O_2$ 269.389 g/mol	**Rolziracetam** 18356-28-0 $C_7H_9NO_2$ 139.154 g/mol

		
Seletracetam	**Sunifiram**	**Unifiram**
357336-74-4 $C_{10}H_{14}F_2N_2O_2$ 232.231 g/mol	314728-85-3 $C_{14}H_{18}N_2O_2$ 246.31 g/mol	272786-64-8 $C_{13}H_{15}FN_2O_3S$ 298.332 g/mol

Aniracetam

Synonyms: 1-[(4-Methoxybenzoyl)]-2-pyrrolidinone; 1-(4-methoxybenzoyl)pyrrolidin-2-one; Ro 13-5057; Draganon; Sarpul; Ampamet; Memodrin; Referan; 1-*p*-anisoyl-2-pyrrolidinone

Aniracetam is an ampakine nootropic derived from the racetam class of drugs, and shares a similar chemical structure with piracetam. Aniracetam has possible cognition enhancing effects.

Aniracetam is considered to be substantially more potent (likely due to its lipid solubility) than piracetam. Like piracetam, aniracetam modulates of the acetylcholine system and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Aniracetam possesses a wide range of anxiolytic properties, which may be mediated by an interaction between cholinergic, dopaminergic and serotonergic systems. Aniracetam is reported to preserve cognitive function in people with dementia.

Aniracetam is suspected of being a reproductive toxin, damaging fertility or the unborn child.

Reports indicate that aniracetam is no longer in clinical use.

Coluracetam

Synonyms: N-(2, 3-Dimethyl-5, 6, 7, 8-tetrahydrofuro [2, 3-b] quinolin-4-yl)-2-(2-oxo-1-pyrrolidinyl) acetamide; MKC-231; bci-540

Coluracetam is a nootropic agent of the racetam family. Coluracetam is a chemical analogue of piracetam.

Coluracetam boosts choline conversion to acetylcholine in the brain through the high affinity choline uptake (HACU) process and is reported to be a potential therapeutic drug for schizophrenia.

Dimiracetam

Synonyms: Neurotune; 3,6,7,7a-tetrahydro-1H-pyrrolo[1,2-a]imidazole-2,5-dione; Dihydro-1H-pyrrolo(1,2-a)imidazole-2,5(3H,6H)-dione

Dimiracetam has been shown to have a beneficial effect on peripheral neuropathic pain in rats.

Fasoracetam

Synonyms: (5R)-5-(piperidine-1-carbonyl) pyrrolidin-2-one; NS-105; N-(5-Oxo-D-prolyl) piperidine; Ichem

Fasoracetam is a nootropic and cognitive enhancer.

Fasoracetam stimulates adenylate cyclase, leading to increased cyclic adenosine monophosphate (cAMP) formation, which is implicated in a variety of signal transduction processes such as learning and memory. It mitigated deficits in learning and memory induced by baclofen in rats Fasoracetam was originally developed by Nippon Shinyaku in search for the treatment of Alzheimer's disease, and has been in clinical trials for vascular dementia and attention deficit hyperactivity disorder.

Methylphenylpiracetam

Synonyms: 2-(5-Methyl-2-oxo-4-phenyl-pyrrolidin-1-yl)-acetamide; 2-[(2S, 3R)-2-methyl-5-oxo-3-phenylpyrrolidin-1-yl] acetamide

Methylphenylpiracetam is the methylated form of piracetam and a positive allosteric modulator of the sigma-1 receptor. Methylphenylpiracetam has shown to enhance cognition and efficacy against cholinergic dysfunction in mice. Methylphenylpiracetam is more potent that phenyl piracetam.

Nebracetam

Synonyms: 4-(aminomethyl)-1-benzylpyrrolidin-2-one ; (RS)-4-(Aminomethyl)-1-benzylpyrrolidin-2-one; Web-1881-FU; -Benzyl-4-aminomethyl-pyrrolidin-; Nebracetamum

Nebracetam is a M1 acetylcholine receptor agonist in rats. A small study in humans has shown that nebracetam may have potential in treating Alzheimer’s disease. Nebracetam activates the cholinergic system, resulting in Alzheimer symptom improvement.

Nefiracetam

Synonyms: *N*-(2, 6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl) acetamide; Translon; DM 9384; DMPPA; Motiva; DZL-221; Nefiracetamum;

Nefiracetam is a nootropic drug of the racetam family. Animal studies show that nefiracetam may have anti-dementia properties as well as anti-amnesic effects against a number of memory impairing substances.

Nefiracetam is thought to be an agonist of the GABA-A receptor. Nefiracetam was able to reverse picrotoxin and bicuculline-induced amnesia in mouse models.

Nefiracetam causes renal and testicular toxicity in dogs and rats. There was no evidence of toxicity in humans during clinical trials.

Omberacetam

Synonyms: Noopept; ethyl 2-[[(2S)-1-(2-phenylacetyl) pyrrolidine-2-carbonyl] amino] acetate; *N*-Phenylacetyl-L-prolylglycine ethyl ester; GVS-111; ethyl phenylacetyl-Pro-Gly; Glycine, 1-(phenylacetyl)-L-prolyl-, ethyl ester

Omberacetam (also commonly known as Noopept) is a nootropic molecule that demonstrates a wide spectrum of cognition improving effects and neuroprotective properties. Omberacetam also shows promise in Alzheimer's disease. Compared to piracetam, omberacetam is more potent, producing a cognition enhancing effect at much lower concentrations.

Oxiracetam

Synonyms: 2-(4-hydroxy-2-oxopyrrolidin-1-yl)acetamide; ISF 2522; 4-Hydroxy-2-oxopyrrolidine-N-acetamide; Hydroxypiracetam; Neuromet; Neuractiv; CT-848; Oxiracetamum

Oxiracetam is a nootropic drug of the racetam family and the hydroxylated analogue of piracetam. These chemicals share a similar structure and both are considered cognitive enhancers. Oxiracetam is also a very mild stimulant. Research suggests that oxiracetam is a more powerful cognitive enhancer than piracetam.

Oxiracetam activates amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-type glutamate receptors, but not kainate or NMDA receptors, in neuronal cultures. This action increases the density of receptor binding sites for AMPA and increases neuronal intracellular calcium concentrations.

Reports indicate that oxiracetam is no longer in clinical use. Prior to 1999 there were 22 clinical trials on oxiracetam.

Oxiracetam was developed by SIF, Italy but is no longer available from the supplier. The product insert states that oxiracetam is for "*mental syndromes caused by cerebral insufficiency, disturbances in mental performance in the elderly, and no adverse interactions have been noted*".

Adverse effects of oxiracetam include psychomotor excitability and sleep disorders.

Phenylpiracetam

Synonyms: Fonturacetam; 2-(2-oxo-4-phenylpyrrolidin-1-yl)acetamide; 4-Phenyl-2-pyrrolidone-1-acetamide; Carphedon; Karfedon; BRN 5030440; J-500892; Phenotropil

Phenylpiracetam, is the phenylated analogue of piracetam, and is also considered a cognitive enhancer. Phenylpiracetam is absorbed rapidly and exhibits high oral bioavailability. Phenylpiracetam is reported to be more potent, and is used for a wider range of indications than piracetam.

Phenylpiracetam is reportedly beneficial to people who develop cognitive deficits and/or depression after encephalopathy and brain injuries. It was reported to increase quality of life in patients with encephalopathy after acute lesions, brain traumas and glioma surgery.

Phenylpiracetam was developed by Medical-Biological Institute of the Russian Academy (manufactured by Valenta Pharmaceuticals in Russia). In 2003, the State Pharmacological Committee of Russia approved phenylpiracetam as a prescription drug for cerebrovascular deficiency, depression, apathy, attention and memory decline, and it is recommended for cosmonauts for increasing physical and mental/cognitive activities in space.

Adverse events associated with phenylpiracetam use include sleep disturbance.

Pramiracetam

Synonyms: N-[2-(Diisopropylamino)ethyl]-2-(2-oxopyrrolidin-1-yl)acetamide; Pramistar; amacetam; Pramiracetamum; Vinpotropil; Neupramir; Q-201610; CNS-1879; Ectapram; CI-879

Pramiracetam is a central nervous system stimulant and nootropic agent belonging to the racetam family of drugs, which shares a similar chemical structure with piracetam. Pramiracetam is considered to be 30 times stronger than piracetam and reportedly improves cognitive deficits associated with traumatic brain injuries.

Pramiracetam increases the rate of sodium-dependent high-affinity choline uptake in rat hippocampal synaptosomes *in vitro*, and it is proposed that its effect on cognitive functions might occur via acceleration of cholinergic transmission in the septal-hippocampal region.

Prior to 1999 there were four clinical trials on pramiracetam. Pramiracetam was developed by Warner-Lambert, USA. Adverse effects include insomnia, dysphoria, gastralgia and heartburn.

Rolziracetam

Synonyms: 2, 6, 7, 8-tetrahydro-1H-pyrrolizine-3, 5-dione; CI-911; 3, 5-Dioxopyrrolizidine; Rolziracetamum; NSC-122751

Rolziracetam has been shown to improve performance of a delayed-response task in aged Rhesus monkeys. As a result, this drug was proposed as a good candidate for the treatment of cognitive impairment in humans. However, further development has slowed due to its instability in plasma (half-life <25 minutes).

Seletracetam

Synonyms: (2S)-2-[(4S)-4-(2, 2-difluoroethenyl)-2-oxopyrrolidin-1-yl] butanamide; UCB-44212

Seletracetam, like the Schedule 4 substances brivaracetam and levetiracetam, is considered an antiepileptic and anticonvulsive drug. Seletracetam binds to synaptic vesicle 2A (SV2A) protein in brain membranes and fibroblasts with high affinity.

Sunifiram

Synonyms: 1-(4-benzoylpiperazin-1-yl) propan-1-one; 1-Benzoyl-4-propanoylpiperazine; DM-235; CS-2193

Sunifiram (1-benzoyl-4-propionylpiperazine) is a synthetic derivative of piracetam. These chemicals are structurally different; however sunifiram is still considered a piracetam-like nootropic, and is derived from the racetam class of drugs.

Sunifiram is 10,000 times more potent than piracetam, and is used as a cognitive enhancer.

There have been reported cases in the UK of sunifiram being used as a 'smart drug'. Students have also been found to be 'stacking' a variety of nootropic medicines, obtaining them illegally from online suppliers without prescription.

Unifiram

Synonyms: 2-(4-fluorophenyl) sulfonyl-1, 3, 4, 7, 8, 8a-hexahydropyrrolo [1, 2-a] pyrazin-6-one; DM-232;

Like sunifiram, unifiram is also considered a piracetam-like nootropic, derived from the racetam class of drugs. Unifiram is more potent that piracetam and has anti-amnesic and other effects in animal studies.

As of 2015, no formal human studies with unifiram have been conducted. Unifiram is not patented and, despite the lack of human and long-term toxicity studies, it is commonly sold online.

Pre-meeting public submissions

Two public submissions were received before the first closing date in response to an invitation published on 31 August 2018 under regulation 42ZCZK of the Regulations.

Both public submissions supported the scheduling proposal.

The main points provided in support of the amendment were:

- Due to the potential use and adverse events it is appropriate to make these medicines prescription only.

- It will strengthen the way all racetam substances are captured in the Poisons Standard and improve clarity of entries.
- Clarification is sought on the basis for inclusion of substances; for example, etiracetam (CAS number 33996-58-6) is not included on the list.

ACMS advice

The committee recommended that a new Schedule 4 group entry for racetams be established, with new specific Schedule 4 entries for aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram, with a new Appendix K entry for seletracetam in the Poisons Standard as follows:

Schedule 4 – New/Entries

RACETAMS

except when separately specified in these Schedules.

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COLURACETAM.

DIMIRACETAM.

FASORACETAM.

METHYLPHENYLPIRACETAM.

NEBRACETAM.

NEFIRACETAM.

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Appendix K – New entry

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METHYLPHENYLPIRACETAM
cross reference: RACETAMS

Schedule 4

NEBRACETAM
cross reference: RACETAMS

Schedule 4

NEFIRACETAM
cross reference: RACETAMS

Schedule 4

OMBERACETAM
cross reference: RACETAMS

Schedule 4

OXIRACETAM
cross reference: RACETAMS

Schedule 4

PHENYLPIRACETAM
cross reference: RACETAMS

Schedule 4

PRAMIRACETAM
cross reference: RACETAMS

Schedule 4

ROLZIRACETAM
cross reference: RACETAMS

Schedule 4

SELETRACETAM
Cross reference RACETAMS
Schedule 4
Appendix K

Schedule 4

SUNIFIRAM
cross reference: RACETAMS

Schedule 4

UNIFIRAM
cross reference: RACETAMS

The committee also recommended an implementation date of **1 June 2019**.

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

The reasons for the advice included:

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

- The substances are claimed to be memory enhancers but only based on animal studies.
- The risk is that the substances are being used by healthy individuals, with potential acute and long term harm.
- Racetams are nootropic agents. There is worldwide interest in nootropics for treatment of CNS disorders including epilepsy, dementia, stroke, ischaemia and stress. They are also used in efforts to restore memory and brain performance in encephalopathies including cranial traumas and inflammation. Those that remain in development and clinical use seem to be well tolerated with low potential for drug interactions.
- With increasing ageing population and incidence of degenerative disorders (dementias) clinical trials with this group of substances and their derivatives are likely to continue. This clinical use justifies prescription medicine status.

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

- Nootropics are used clinically for treatment of CNS disorders including epilepsy, dementia, stroke, ischaemia and stress.
- They are also used in efforts to restore memory & brain performance in encephalopathies including cranial traumas and inflammation.
- Other than brivaracetam, levetiracetam and piracetam, none of the racetams are in any products on the ARTG.

(c) the toxicity of a substance:

- Toxicity is poorly studied, but some cause psychomotor agitation, dysphoria, insomnia, heartburn, stomach pain, which are likely to occur with all the 'cognitive enhancers'.
- Long term effects are not known but potential reproductive, testicular, gastrointestinal and renal toxicity has been seen in animals.
- Low toxicity in those currently still available in clinical use. Those no longer in clinical use have greater toxicity e.g. aniracetam is suspected of being a reproductive toxicant.

- Brivaracetam and levetiracetam are listed in Appendix K (sedation warning). This could be considered for seletracetam as it is similar to brivaracetam and levetiracetam and similarly considered an anticonvulsant with somnolence reported as common AE in Phase II trials.

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

- No products containing the 15 racetams (aniracetam, coluracetam, dimiracetam, fasoracetam, methylphenylpiracetam, nebracetam, nefiracetam, omberacetam, oxiracetam, phenylpiracetam, pramiracetam, rolziracetam, seletracetam, sunifiram and unifiram) are approved therapeutic substances in Australia and are not in any therapeutic goods on the Australian Register of Therapeutic Goods.

(e) the potential for abuse of a substance

- No evidence for dependence or abuse, rather use without evidence of efficacy.
- Low but some reports of obtaining racetams online as 'smart drugs' for cognition enhancement or supplements for memory performance.

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

- Nil.

2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS/ACMS #20)

2.1 Salts of boric acid

Delegate's interim decision

Interim decision:

The delegate's interim decision under regulation 42ZCZN of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to boric acid and it salts.

The amendments relate to the delegate's final decision (published on 10 April 2018) to amend the Schedule 5 entry for boric acid aligning it with the European Union cut-off concentrations for cosmetics, to create new entries in Schedule 5 for the salts of boric acid (due to be implemented on 1 June 2019) and to create new Appendix F, Part 3 entries, as follows:

Schedule 5

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)~~ cosmetic hand cleaning preparations when labelled with a warning to the following effect:

NOT TO BE USED FOR CHILDREN UNDER 3 YEARS OF AGE; and if the concentration of free soluble borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

c) ~~d)~~in cosmetic talc preparations containing 5 ~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; and if the concentration of free soluble borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) ~~e)~~in cosmetic oral hygiene preparations containing 0.1~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. ~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; or

e) ~~f)~~in other cosmetic preparations containing 3~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; and if the concentration of free soluble borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

f) in preparations, other than insect baits, containing 6 per cent or less calculated as boric acid.

~~**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~~

Appendix E, Part 2

BORIC ACID

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)).

Appendix F, Part 3 – New Entry

BORIC ACID when included in Schedule 5

Warning statements:

25 (Do not use on broken skin. Wash hands thoroughly after use); and

26 (powder) (and) (concentrated solutions) are dangerous if swallowed

Index – Amend Entry

BORIC ACID cross reference: BORAX

Schedule 4

Schedule 5

Appendix E, Part 2

Appendix F, Part 3

Proposed date of effect of the proposed amendment: **1 February 2020**

Reasons for interim decision:

The reasons for the interim decision are as follows:

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

Salts of boric acid are used as excipients in a range of therapeutic goods, cosmetics and other domestic and industrial products. They are also used as both active ingredients and excipients in a range of veterinary medicines and pesticide products.

While salts of boric acid are considered to have low to moderate effects in humans with normal use, they can still however cause minor adverse effects.

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 very low concentrations in cosmetics as buffering/viscosity controlling agents, as enzyme stabilisers in domestic detergent products and as corrosion inhibitors in industrial products. Salts of boric acid are also used in personal care products (e.g. antiseptics, astringents, skin lotions, eyewash solutions).

Salts of boric acid are also used in a range of professional and domestic animal treatment products (e.g. poultices, ear cleaners, wound ointments), insecticide products and swimming pool products (e.g. bactericides, algaecides).

Borax can be purchased from Australian supermarkets and from online retailers.

Boric acid is also an ingredient in a range of therapeutic products including eye drops, antifungal treatments, contact lens solution, detergents and vitamins.

c. the toxicity of a substance:

The main toxicological concern for boric acid and its salts in animal studies is the potential to cause reproductive and developmental effects. Testes and the developing fetus have been identified as the most sensitive targets of boron toxicity in animal studies.

The data for oral, dermal and inhalation toxicity and genotoxicity or carcinogenicity in humans are limited or non-existent and overall, toxicity was considered to be low. No appropriate toxicological data are available for analogues boric acid and borax.

Although no information is available on the skin sensitisation potential of chemicals in this group, based on the available information on the analogue chemicals, the chemicals in this group are not likely to be skin sensitisers.

The limited data indicate that the chemicals in this group are unlikely to be specific respiratory irritants.

The compounds in this group (including, tetraborates, and octaborates as well as the other boric acid salts/esters (MEA-borate, MIPA-borate, potassium borate, trioctyldodecyl borate and zinc borate) produce boric acid following contact with water.

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

All products captured by the Schedule 5 entry for boric acid should be labelled with appropriate warning statements as dictated by the toxicological profile for boric acid (specifically warnings against use in young children due to potential for developmental and reproductive toxicity, and warnings not to use on broken, peeling or irritated skin).

e. the potential for abuse of a substance:

Nil.

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

Nil.

Overall conclusions

In November 2017, the Joint ACMS-ACCS considered an application to amend the current entry for boric acid in Schedule 5, to remove 'excluding its salts', so that salts of boric acid are captured by the Poisons Standard. On the 10 April 2018 the delegate published a final decision to amend the Schedule 5 entry for boric acid to align it with European Union concentrations for cosmetics, and to create new entries in Schedule 5 for salts to address risks identified by the NICNAS IMAP assessment, with an implementation date of 1 June 2019. However, the amended entry contained inconsistencies with overseas requirements for cosmetics which may have unintentionally affected non-cosmetic products. In addition, the entry did not address the need to restrict access in children, or include appropriate warnings for repeated use, ingestion and developmental and reproductive toxicity**.**

This interim decision to amend the Poisons Standard with respect to salts of boric acid is to clarify the nature of the amendments to the entry to ensure that it is clear and unambiguous, is consistent with overseas requirements and does not inadvertently disadvantage legitimate safe use of boric acid and its salts and related products.

Materials considered

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

- The Delegate's final decision, published on 10 April 2018 to amend the current Poisons Standard with respect to salts of boric acid;
- The public submissions received before the first closing date;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #20);

- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal for salts of boric acid was published on the TGA website on 31 August 2018 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2018.

Background information for salts of boric acid

The delegate of the Secretary sought advice from the Joint Advisory Committees on Chemicals Scheduling (ACCS) and Advisory Committee on Medicines Scheduling (ACMS) on a proposal to amend the Poisons Standard with respect to boric acid and its salts. The proposed amendments relate to the final decision (published on 10 April 2018) to amend the Schedule 5 entries for boric acid and its salts (due to be implemented on 1 June 2019) and to create new Appendix F, Part 3 entries.

Purpose: to clarify the nature of the amendments to the entries to ensure that they are clear and unambiguous and do not inadvertently disadvantage legitimate safe use of Boric Acid and related products.

Scheduling proposal and reasons

The delegate's proposed amendments to the Poison Standard[17] are:

Schedule 5 - Amend Entry

BORIC ACID **except**:

a) when included in Schedule 4; or

b) in preparations, other than insect baits, containing 1 per cent or less calculated as boron; or

c) in hand cleaning preparations when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

[17] This proposed amendment refers to the delegate's final decision, published on 10 April 2018

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

NOT TO BE SWALLOWED. DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN UNDER 3 YEARS; or

f) in other preparations, other than insect baits, 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

Index - Amend Entry

BORIC ACID
cross reference: BORAX, BORON, SODIUM BORATE, POTASSIUM BORATE, MEA-BORATE AND MIPA-BORATE

Schedule 5 - New Entries

SODIUM BORATE (CAS No. 1330-43-4) **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 when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

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

NOT TO BE SWALLOWED. DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN UNDER 3 YEARS; or

f) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

POTASSIUM BORATE (CAS No. 1332-77-0) **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 when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

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

NOT TO BE SWALLOWED. DO NOT USE (THIS PRODUCT/INSERT NAME OF PRODUCT) IN CHILDREN UNDER 3 YEARS; or

f) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

MEA-borate (CAS No. 26038-89-9) **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 when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

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

NOT TO BE SWALLOWED. DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; or

f) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

MIPA-BORATE (CAS No. 26038-90-4 and 68003-13-4) **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 when labelled with a warning to the following effect:

DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

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

NOT TO BE SWALLOWED. DO NOT USE (THIS PRODUCT/*INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS; or

f) 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 UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

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. 26038-89-9)

Schedule 5

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

Schedule 5

Appendix F, Part 3 - New Entry

BORIC ACID, SODIUM BORATE, POTASSIUM BORATE, MEA-BORATE AND MIPA-BORATE when included in Schedule 5

Warning statements:

- 25 (Do not use on broken skin. Wash hands thoroughly after use); and
- 26 (powder) (and) (concentrated solutions) are dangerous if swallowed; and
- 38 (CAUTION - Do not use for children under 2 years unless a doctor has told you to; and
- 77 (may cause birth defects) or 46 (WARNING - contains boric acid which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with boric acid).

Current scheduling status

On the 10 April 2018 the delegate published a final decision to amend the Schedule 5 entry for boric acid aligning it with European Union cut-off 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)

Scheduling history

The scheduling history for boron compounds dates back to July 1968. The most recent scheduling considerations are as follows:

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

The May and August 2001 NDPSC Meetings agreed to revise the boron Schedule 4 entry to exempt a daily oral dose of 3 mg and to exempt dermal preparations containing 0.35 per cent or less to harmonise with the New Zealand (NZ) classification for dermal use. However, the committee did not agree to harmonise on other use patterns. This outcome was referred to NZ's Medicines Classification Committee (MCC) for consideration.

February 2006 National Drugs and Poisons Schedule Committee (NDPSC)

The February 2006 NDPSC Meeting:

- noted that NZ had toxicity concerns regarding the use of high strength boron for nappy rash in babies under occlusive conditions.
- noted that NZ products only contained boric acid and that boron was not listed as an ingredient in medicines. In contrast, registered ingredients for Australian therapeutic products include either boron or boric acid. A Member also noted that the boron scheduling excluded excipients and that this may need to be reviewed on the basis of the substance's toxicity.
- recommended that NZ consider harmonising with the Australian scheduling of boron and that MCC consider submitting a proposal to the NDPSC regarding appropriate nomenclature for harmonisation.

June 2007 National Drugs and Poisons Schedule Committee (NDPSC)

The June 2007 NDPSC Meeting agreed that consideration of the scheduling of boron should be deferred, pending information from NZ regarding a potential proposal to set a new exemption cut-off, and the reasons for any such recommendation.

December 2007 NZ Medicines Classification Committee (MCC)

At the December 2007 Meeting, the MCC agreed that boron, including boric acid and borax, should be a prescription medicine except when for internal use in medicines containing 6 mg or less per recommended daily dose; for dermal use other than paediatric use, in medicines containing 0.35 per cent or less or when present as an excipient.

February and June 2008 National Drugs and Poisons Schedule Committee (NDPSC)

At the February and June 2008 NDPSC Meetings, following reconsideration of the issues (including the reasons for the adoption by New Zealand of a 6 mg cut-off for internal use), it was agreed to foreshadow the following amendments to the Schedule 4 boron entry (including capturing of all paediatric use as Schedule 4) to allow stakeholders a further opportunity to comment, and to help identify any potential unintended consequences:

- Broadening the entry, particularly regarding topical use, by amending from an inclusive to an exclusive form.
- Increasing the internal use cut-off from 3 mg to 6 mg.
- Capturing all dermal paediatric use in Schedule 4 (i.e. remove the current allowance for dermal paediatric use, when not a dusting powder and ≤ 0.35 per cent, to be unscheduled).
- Removing the exemption for antifungal preparations for dermal use (i.e. these will be captured in Schedule 4).
- Adding the expression "including boric acid and borax" and changing 'milligrams' in part (a) to 'mg'.

"Schedule 4 – Foreshadowed amendment

BORON – Amend entry to read:

BORON, including boric acid and borax, for human therapeutic use ***except****:*

a) in preparations for internal use containing 6 mg or less of boron per recommended daily dose;

b) in preparations for dermal use containing 0.35 per cent or less of boron, other than preparations other than preparations for paediatric or antifungal use; or

c) when present as an excipient."

(The above Schedule 4 amendment was implemented in the Poisons Standard on 1 January 2009).

November 2017 Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS)

In November 2017, the Joint ACMS-ACCS considered an application to amend the current entry for boric acid in Schedule 5, to remove "excluding its salts", so that salts of boric acid are captured by the Poisons Standard. On the 10 April 2018 the delegate published a final decision to amend the Schedule 5 entry for boric acid to 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, with an implementation date of 1 June 2019.

Australian regulations

Boric acid is an ingredient in 80 products on the ARTG including eye drops, antifungal treatments, contact lens solution, detergents and vitamins.

Boric acid is listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2018 as follows:

	Ingredient Name	Purpose of the ingredient in the medicine	Specific requirements
903	BORIC ACID	A, H	Boron is a mandatory component of Boric acid. The percentage of Boron from Boric acid should be calculated based on the molecular weight of Boric acid. The maximum recommended daily dose must provide no more than 6 mg of Boron. In preparations for dermal use, which are not for paediatric or antifungal use, the concentration of boron in the medicine must be no more than 3500 mg/kg or 3500 mg/L or 0.35%.

Some members of this group (CAS Nos. 1330-43-4, sodium borate; 12267-73-1, tetraboron disodium heptaoxide; 13840-56-7, sodium orthoboric acid) are classified as hazardous for reproductive and developmental toxicity – Category 1B; H360FD (May damage fertility. May damage the unborn child) in the HCIS (Safe Work Australia).

Boric acid (CAS No. 10043-35-3) is classified as hazardous for reproductive and developmental toxicity – Category 1B; H360FD (May damage fertility. May damage the unborn child) in the HCIS (Safe Work Australia).

International regulations

European Union (EU)

EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products—Annex III— "List of substances which cosmetic products must not contain except subject to the restrictions laid down" with specific conditions on maximum in-use concentrations for:

- talc (5%);
- oral products (0.1%); and
- other products (3%) (excluding bath products and hair waving products).

Talc products are not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1.5% (as boric acid), and must be labelled as follows:

- Not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin.

Oral products are not to be used in products for children under 3 years of age, and must be labelled as follows:

- Not to be swallowed. Not to be used in products for children under 3 years of age.

Other products are not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin if the concentration of free soluble borates exceed 1.5% (as boric acid), and must be labelled as follows:

- Not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin.

The 2013 EU SCCS opinion on "the safety of boron compounds in cosmetic products" recommended further risk management. However this recommendation has not yet been implemented in legislation.

Canada

The chemicals boric acid, disodium salt, MEA-borate and MIPA-borate are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Substance summary

European Union (EU)

EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products—Annex III— "List of substances which cosmetic products must not contain except subject to the restrictions laid down" with specific conditions on maximum in-use concentrations for:

- talc (5%);
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- Not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin.

Oral products are not to be used in products for children under 3 years of age, and must be labelled as follows:

- Not to be swallowed. Not to be used in products for children under 3 years of age.

Other products are not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin if the concentration of free soluble borates exceed 1.5% (as boric acid), and must be labelled as follows:

- Not to be used in products for children under 3 years of age. Not to be used on peeling or irritated skin.

The 2013 EU SCCS opinion on "the safety of boron compounds in cosmetic products" recommended further risk management. However this recommendation has not yet been implemented in legislation.

Canada

The chemicals boric acid, disodium salt, MEA-borate and MIPA-borate are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Pre-meeting public submissions

One public submission was received before the first closing date in response to an invitation published on 31 August 2018 under regulation 42ZCZK of the Regulations.

The submission recommended changes to the scheduling proposal to increase alignment with EU cosmetic regulations while retaining current levels of availability for other uses. The main points of the submission were:

- Boric acid and the four borate salts are used in very low concentrations in cosmetics as buffering/viscosity controlling agents (sodium borate), as enzyme stabilisers in domestic detergent products and as corrosion inhibitors in industrial products.
- Inclusion of the word "cosmetic" in the exemptions for talc, oral and other cosmetic preparations, as these align with the EU Cosmetics regulation and should only apply to cosmetic products.
- Clarification that the cut-off concentrations for the cosmetic exemptions is calculated as that of boric acid (not boron as currently proposed) to align with the EU Cosmetics regulation.
- Removal of the words "(*THIS PRODUCT/INSERT NAME OF PRODUCT*)" from the warning statements, as this is unnecessary, does not add any benefit, and is additional to what is required overseas.
- Correction of substance names in the entries for potassium borate, MEA borate and MIPA borate. (The Secretariat has corrected these typographic errors).
- There are concerns with the proposed new Appendix F entry for these substances, as the warning statements proposed are not consistent with the schedule entries for these substances e.g.:

- The warning statement "DO NOT USE (*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS" is required to meet the exemptions for cosmetic products, but if this statement is not applied, then the preparation is a Schedule 5 poison and the Appendix F statement of "CAUTION - Do not use for children under 2 years unless a doctor has told you to" applies. This is not consistent and does not make sense and should therefore be amended for consistency or removed.
- The proposed Appendix F warning statements do not seem consistent with the risk profile of a Schedule 5 substance:
  - 77 (may cause birth defects) or
  - 46 (WARNING - contains boric acid which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with boric acid)

- Currently, these statements only apply to Schedule 4 and Schedule 7 substances. The previous final decision for these substances noted: *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.* These statements should therefore be reviewed or removed.
- Depending on the extent of any changes, an adequate transition period will be required to allow for any reformulation and/or labelling changes that would be required for products already in the Australian market.

The following changes to the proposed scheduling entries were proposed:

Schedule 5 - Amended entries

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 when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT*~~/INSERT NAME OF PRODUCT~~)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

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

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

e) in cosmetic oral ~~hygiene~~ preparations containing 0.1% or less ~~calculated as boric acid~~ when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; or

f) in other cosmetic preparations~~, other than insect baits,~~ containing 3% or less ~~calculated as boric acid~~ when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

Schedule 5 - New Entries
SODIUM BORATE (CAS No. 1330-43-4) **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 when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) in cosmetic talc preparations containing 5% or less of sodium borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

e) in cosmetic oral hygiene preparations containing 0.1% or less of sodium borate (calculated as boric acid) when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; or

f) in other cosmetic preparations containing 3% or less of sodium borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN CHILDREN UNDER 3 YEARS~~; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

POTASSIUM BORATE (CAS No. 1332-77-0) **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 when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) in cosmetic talc preparations containing 5% or less of potassium borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

e) in cosmetic oral hygiene preparations containing 0.1% or less of potassium borate (calculated as boric acid) when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; or

f) in other cosmetic preparations containing 3% or less of potassium borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

MEA-borate (CAS No. 26038-87-9) **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 when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) in cosmetic talc preparations containing 5% or less of MEA-borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

e) in cosmetic oral hygiene preparations containing 0.1% or less of MEA-borate (calculated as boric acid) when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; or

f) in other cosmetic preparations containing 3% or less of MEA-borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

MIPA-BORATE (CAS No. 26038-90-4 and 68003-13-4) 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 when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) in cosmetic talc preparations containing 5% or less of MIPA-borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN); or

e) in cosmetic oral hygiene preparations containing 0.1% or less of MIPA-borate (calculated as boric acid) when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. DO NOT USE ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*)~~ IN CHILDREN UNDER 3 YEARS; or

f) in other cosmetic preparations containing 3% or less of MIPA-borate (calculated as boric acid) when labelled with a warning to the following effect:

DO NOT USE ~~(THIS PRODUCT/INSERT NAME OF PRODUCT)~~ IN CHILDREN UNDER 3 YEARS; and if the concentration of free soluble borates exceeds 1.5% (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN.

Joint ACMS-ACCS advice

The committee recommended that separate Schedule 5 entries for the salts of boric acid (sodium borate, potassium borate, MEA-borate and MIPA-borate are not necessary as they are captured by the scheduling entry for boric acid (and the words 'excluding its salts' has been removed). Amendments to the delegate's final decision to the Schedule 5 entry for boric acid to align with the cut-offs and wording of warnings in EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products—Annex III— 'List of substances which cosmetic products must not contain except subject to the restrictions laid down' are recommended as follows:

Schedule 5

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) cosmetic hand cleaning preparations when labelled with a warning to the following effect:

NOT TO BE USED FOR CHILDREN UNDER 3 YEARS OF AGE; and if the concentration of free soluble borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

c) ~~d)~~in cosmetic talc preparations containing 5 ~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; and if the concentration of free soluble borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

d) ~~e)~~in cosmetic oral hygiene preparations containing 0.1~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

NOT TO BE SWALLOWED. ~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; or

e) ~~f)~~in other cosmetic preparations containing 3~~%~~ per cent or less calculated as ~~boron~~ boric acid when labelled with a warning to the following effect:

~~DO~~ NOT TO BE USED ~~(*THIS PRODUCT/INSERT NAME OF PRODUCT*) IN~~ FOR CHILDREN UNDER 3 YEARS OF AGE ~~OR LESS~~; and if the concentration of free soluble

borates exceeds 1.5 per cent (as boric acid), with the words: NOT TO BE USED ON PEELING OR IRRITATED SKIN; or

f) in preparations, other than insect baits, containing 6 per cent or less calculated as boric acid.

~~**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) sin 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~~

Appendix E, Part 2

BORIC ACID

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)).

Appendix F, Part 3 – New Entry

BORIC ACID when included in Schedule 5

Warning statements:

25 (Do not use on broken skin. Wash hands thoroughly after use); and

26 (powder) (and) (concentrated solutions) are dangerous if swallowed

Index – Amend Entry

BORIC ACID cross reference: BORAX

Schedule 4

Schedule 5

Appendix E, Part 2

Appendix F, Part 3

In addition, the committee recommended an **implementation date of 1 February 2020**, to allow industry time to comply with any changes in product labelling requirements.

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

The reasons for the advice included:

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

Risks:

Data indicates that the hazard is considered:

- low to moderate effects in humans with normal use
- can cause only minor adverse effects to the human being in normal use;
- requires caution in handling, storage, or use (S5)
- may cause death or severe injury if ingested (S6)

Benefits:

- used as an excipient to improve products

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

- Boric Acid and its salts are used in a wide range of cosmetics and personal products (antiseptics/astringents/skin lotions/some eyewash solutions/enamels and glazes)

- Domestic and industrial cleaning products including dishwashing and laundry liquids.

c) the toxicity of a substance:

- The testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies.
- Humans: No or limited data of oral, dermal and inhalation toxicity and genotoxicity or carcinogenicity. Overall, evidence from studies considered toxicity in these areas low in humans. No appropriate data available for analogues boric acid and borax.
- Salts of boric acid are readily converted to boric acid in aqueous solutions

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

Appropriate warnings to be included for:

- Repeated Use
- Ingestion
- Developmental and Reproductive toxicity
- Labelling and packaging to restrict use in children and child access to products with higher concentrations.

2.2 Naphthalene

Delegate's interim decision

Interim decision:

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

Schedule 10 – New Entry

NAPHTHALENE for domestic use **except** when enclosed in a device which, in normal use, prevents removal or ingestion of its contents.

Index

NAPHTHALENE

Schedule 6

Schedule 10

Appendix E, Part 2

Appendix F, Part 3

Appendix G

Proposed date of effect of the proposed amendment: **1 June 2019**

Reasons for interim decision:

The reasons for the interim decision are as follows:

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

Naphthalene has traditionally been used as the main ingredient in mothballs for home use. Evidence presented indicates that naphthalene balls are sometimes incorrectly labelled as 'camphor', a safer alternative to naphthalene. Use of naphthalene in the domestic environment is associated with the risk of toxicity due to inhalation and ingestion, notably in children. While the risks associated with the use of naphthalene mothballs are significantly mitigated where proper containment is used, continued reports of toxicity indicate current scheduling, labelling and packaging restrictions may be ineffective.

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

Naphthalene has traditionally been used as the main ingredient in mothballs which are used in domestic environments to protect textiles made of natural materials from moth attack. Naphthalene slowly sublimes under ambient conditions and the vapour (the characteristic mothball smell) repels moths.

Naphthalene is also used in plant growth regulators and veterinary parasiticide treatments. However, the major use of naphthalene in Australia is in various industrial products and processes, i.e. as a solvent, in dyes, heat transfer fluid, additives, coatings, textiles, binders, adhesives and surfactants. It is also an impurity in liquid hydrocarbons such as diesel.

c. the toxicity of a substance:

Naphthalene toxicity has been well established and severe toxicity can occur from relatively

small oral or inhaled exposures. Those in the population with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at particular risk, and are usually not aware of this increased individual risk. G6P deficiency is reportedly present in about five per cent of Australians, mainly those of Asian, African, Middle Eastern or Mediterranean descent.

Acute exposure of humans to naphthalene by inhalation, ingestion, and dermal contact is associated with haemolytic anaemia, liver damage, neurological damage in infants, and death.

The US EPA has classified naphthalene as a Group C, possible human carcinogen.

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

The hazard of naphthalene mothballs is recognised within their current scheduling status by the additional requirement that they are contained in a device that prevents ingestion. Naphthalene in ball, block, disc, pellet or flake form for domestic use must be enclosed in a device which prevents removal or ingestion of its contents, is incapable of reacting with the poison, is sufficiently strong, has the word 'POISON' and the name of the poison embossed or indelibly printed on it.

However, evidence shows that this requirement is not being met by all retailers and naphthalene mothballs are freely on sale in loose form, in retail outlets and via the internet and these loose naphthalene balls and flake for domestic use are not legal products. Further, in some cases, these products are packaged and/or coloured in a way that children may mistake them for confectionary.

e. the potential for abuse of a substance:

Cases of naphthalene poisoning in members of the public are regularly reported. Advice from the NSW Poisons Information Centre(PIC) indicates that they still receive calls regarding exposures to naphthalene (92 calls since 2014, 32 requiring hospitalisation) as well as exposures to moth balls of an unknown content, potentially containing naphthalene (113 calls since 2014, 16 requiring hospitalisation). Many of these phone calls involve loose moth balls or parts of moth balls which had escaped the caged packaging designed to prevent exposures.

The taste of naphthalene is not offensive to all people and there are some reports of abuse via deliberate inhalation and ingestion of mothballs. Children have also been known to eat mothballs, and there are case reports of pregnant women sucking on mothballs.

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

Nil

Overall conclusions

Naphthalene is most commonly encountered by the public in the form of mothballs or flakes for the control of moths and larvae which are destructive to natural-fibre textiles. However, naphthalene is predominantly used in Australia as a starting material for, and as a component or natural impurity in a variety of industrial chemicals, dyes, resins, solvents, lubricants and fuel components. In considering the risks and benefits associated with naphthalene, the weight of evidence supports that the major public health risks associated with its use are specifically related to the importation, sale and use of illegal domestic mothball products (i.e. un-registered and un-containerised). To address this non-compliance and significant public health risk the interim decision is targeted to naphthalene mothballs for domestic use that do not meet the Part 2 packaging requirements that are specified in the current Schedule 6 entry for naphthalene in the Poisons Standard.

Materials considered

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

- The application to amend the current Poisons Standard with respect to naphthalene;
- The public submissions received before the first closing date;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #20);
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal for naphthalene was published on the TGA website 31 August 2018 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2018.

Background information for naphthalene

Delegate's referral to ACCS-ACMS

The chemicals scheduling delegate sought advice from the Joint Advisory Committee on Chemical Scheduling (ACCS) and Advisory Committee on Medicine Scheduling (ACMS) on a proposal to reschedule naphthalene from Schedule 6 to Schedule 7 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard.

Applicant's scheduling proposal and reasons

A private applicant submitted a proposal to reschedule naphthalene from Schedule 6 to Schedule 7.

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

Schedule 7 – New Entry

NAPHTHALENE (excluding its derivatives) **except** in liquid hydrocarbons as an impurity.

Schedule 6 – Delete Entry

~~NAPHTHALENE (excluding its derivatives) **except** in liquid hydrocarbons as an impurity.~~

The applicant's reasons for the request are:

- The sale of naphthalene to the public in the form of mothballs is an unacceptable risk. Reports of poisonings in Australia continue and there are regular enquiries to state Poisons Information Centres regarding mothball exposure.
- Sale of naphthalene has been banned in the EU and New Zealand.

- Inhalation of naphthalene vapours can cause toxic reactions and containment in a device that prevents ingestion will not prevent this.
- There are safer alternatives to naphthalene including camphor and 1,4-dichlorobenzene.

Current scheduling status

Naphthalene is currently listed in the Poisons Standard as follows:

Schedule 6

NAPHTHALENE (excluding its derivatives) **except** in liquid hydrocarbons as an impurity.

Appendix E, Part 2

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor at once), G1 (Urgent hospital treatment is likely to be needed), G3 (If swallowed, do NOT induce vomiting)

Appendix F, Part 3

NAPHTHALENE	WARNING STATEMENTS	SAFETY DIRECTION
a) in block, ball, disc, pellet or flake form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents.	9 (Can be fatal to children if sucked or swallowed); 105 (Do not use on the bedding or clothing of infants or in the bedrooms of children 3 years of age or less)	
b) in other forms.	9 (Can be fatal to children if sucked or swallowed); 105 (Do not use on the bedding or clothing of infants or in the bedrooms of children 3 years of age or less)	1 (Avoid contact with eyes)

Appendix G

NAPHTHALENE

Concentration (quantity per litre or kilogram): 1 mg

Naphthalene is also subject to additional labelling and container requirements as outlined in Part 2 of the Poisons Standard as follows:

1.5.9 Camphor and naphthalene

(1) The labelling requirements of Section1.1(2)(d) and Section 1.3 do not apply to a device that contains camphor or naphthalene in block, ball, disc, pellet or flake form if the device:

a) complies with Section 2.7; and

b) is sold or supplied in a primary pack labelled in accordance with Section 1.1 and Section 1.3.

2.7 Camphor and naphthalene

(1) The container requirements of Section 2.1(2) do not apply to a device that contains only camphor or naphthalene in block, ball, disc, pellet or flake form for domestic use, if the device:

a) in normal use, prevents removal or ingestion of its contents; and

b) is incapable of reacting with the poison; and

c) is sufficiently strong to withstand the ordinary risks of handling, storage or transport; and

d) has the word "POISON" and the approved name of the poison embossed or indelibly printed on it.

(2) A person must not sell or supply camphor or naphthalene in ball, block, disc, pellet or flake form for domestic use unless the balls, blocks, discs, pellets or flakes are enclosed in a device which prevents removal or ingestion of its contents.

Scheduling history

February 1987, Drugs and Poisons Schedule Committee (DPSC)

In February 1987 the DPSC reviewed the toxicity of naphthalene in the domestic setting following a discussion of camphor at the November 1986 DPSC meeting. The committee agreed that no action was necessary as naphthalene was appropriately packed and labelled.

August 1989, DPSC (#54)

In August 1989 the DPSC considered a proposal to review the child resistant packaging of naphthalene (and camphor) following an increasing number of reports of poisoning in children. The committee agreed that domestic packs for naphthalene and camphor should be enclosed in child resistant packaging. The following phrase was added to Part 3 of the Poisons Standard:

A person must not sell or supply camphor or naphthalene in ball, block, disc, pellet or flake form for domestic use unless the balls, blocks, discs, pellets or flakes are enclosed in a device which prevents removal or ingestion of its contents.

May 1993, DPSC (#69)

In May 1993 the DPSC considered a proposal to introduce label exemptions for naphthalene (and camphor) and to amend the Schedule 5 entry for naphthalene. The committee recommended that Part 2 of the Poisons Standard be amended as follows:

Camphor and naphthalene

The labelling requirements of Section 3 do not apply to devices enclosing camphor or naphthalene in block, ball, disc or pellet form when sold or supplied in a primary pack which is labelled in accordance with Section 3, provided that they are labelled with:

4.7.1 the word "WARNING";

4.7.2 the approved name of the poison and the quantity or the strength of the poison in accordance with Section 5;and

4.7.3 the name of the manufacturer or distributor or the brand name or trade name used exclusively by a manufacturer or distributor for the poison.

The committee recommended that further review of the Schedule 5 entry for naphthalene to deferred to a future meeting pending advice on the toxicity of naphthalene.

November 1993, DPSC (#91)

At the November 1993 meeting of the DPSC, the committee supported a Drafting Advisory Panel (DAP) proposal, specifying permanent markings (normally placed on a label) on the actual device (used for camphor or naphthalene) in situations where the device, because of its design, could not accept normal labels. The device, which prevents removal of the contents when used correctly, permits the above household chemicals to be classified in Schedule 5 rather than Schedule 6, because of the reduced poisoning potential. The committee recommended the following addition to the Part 2 exemptions for naphthalene and camphor:

Camphor and naphthalene

4.7 The labelling requirements of Sections 1.1.4, 1.3 and 3 do not apply to a device that contains only camphor or naphthalene in block, ball, disc or pellet form, which in normal use prevents removal or ingestion of its contents, when sold or supplied in a primary pack labelled in accordance with Section 3, provided that the device is labelled or embossed legibly with,

4.7.1 the word "WARNING";

4.7.2 the approved name of the poison and the quantity or the strength of the poison in accordance with Section 5; and

4.7.3 the name of the manufacturer or distributor or the brand name or trade name used exclusively by a manufacturer or distributor for the poison.

April 1994, National Drugs and Poisons Schedule Committee (NDPSC #1)

In April 1994, the NDPSC considered and agreed with a proposal to exempt devices containing camphor and naphthalene from some labelling requirements and requiring them to have the name of the poison and the word "WARNING" embossed on the device. The committee, taking into account the toxicity of camphor and naphthalene, also recommended the following:

- The current Appendix F entries for camphor and camphor blocks be combined whilst leaving the entry for camphor for external use to remain unchanged.
- The current Appendix F entry for naphthalene include the warning "Can be fatal to children if sucked or swallowed."
- In the Appendix E entry for naphthalene, the first aid statement "a" to be replaced by statement "i", because of the need to get to a hospital quickly, following ingestion of naphthalene.
- That because 100 mg of naphthalene can be lethal in children and because camphor is also toxic a change in schedule (to S6) be foreshadowed and gazetted for comment and consultation.

August 1994, NDPSC (#2)

At the August 1994 meeting of the NDPSC, the committee considered recommendations on naphthalene and camphor foreshadowed at the April 1994 meeting and subsequently gazetted for public consultation. In relation to naphthalene the committee reaffirmed its support for a Schedule 6 classification but sought further details of products marketed, other than naphthalene as such. It was considered that lower strengths or child resistant packaging would be grounds for lower scheduling classification. It was agreed that following receipt of the above information, the matter would be dealt with out of session.

It was noted that with the foreshadowed recommendation to move this poison from Schedule 5 to Schedule 6, it would be necessary to also exempt the devices from the packaging provisions of Sections 7 and 10.The committee recommended the following amendments to the Poisons Standard:

Poisons Standard Part 2, Section 4 - Amendment

Amend subsection 4.7 to read:

4.7 The labelling requirements of Section 1.1.4, 1.3 and 3 do not apply to a device that contains only camphor or naphthalene in block, disc, or pellet form ifthe device:

4.7.1 complies with Section 12.2;and

4.7.2 is sold or supplied in a primary pack labelled in accordance with Section 3.

Poisons Standard Part 2 - New Entry

12.2 The container requirements of Sections 7 and 10 do not apply to a device that contains only camphor or naphthalene in block, disc or pellet form for domestic use, if the device:

12.2.1 in normal use, prevent removal or ingestion of its contents;

12.2.2 is incapable of reacting with the poison;

12.2.3 is sufficiently strong to withstand the ordinary risks of handling, storage or transport; and

12.2.4 has the word "WARNING" and the approved name of the poison embossed or indelibly printed on it.

APPENDIX F, Part 3 – Amendment Appendix F, Part 3

Naphthalene

a) in block, ball, disc, pellet or flake form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents.in block, ball, disc, pellet or flake form, enclosed in a device which, in normal use, prevents removal or ingestion of its contents.

Warning Statement 9

b) in other forms.

Warning Statement 9

Safety Direction 1

November 1994, NDPSC (#3)

At the November 1994 meeting of the NDPSC, the committee reaffirmed the Schedule 6 recommendation for naphthalene made at the August 1994 meeting on the basis of acute toxicity of naphthalene in humans (oral lethal dose in a child of 100 mg/kg), in the absence of comments arising from the gazettal of the proposal. The committee recommended the following amendment:

Schedule 5 – Amendment

NAPHTHALENE – delete entry

Schedule 6 – New Entry

NAPHTHALENE.

August 1995, NDPSC (#6)

At the August 1995 NDPSC, the Drafting Advisory Panel was requested to revise the proposed Schedule 6 entry for naphthalene as the proposal would automatically include its derivatives and preparations, whereas the original Schedule 5 entry specifically excluded these derivatives. The Committee agreed that the intention of the proposal for Schedule 6 was to include preparations but exclude derivatives and recommended the revised wording be adopted. The committee recommend that the Schedule 6 entry for naphthalene include the phrase '*excluding derivatives)'.*

February 2001, NDPSC (#30)

At the February 2001 meeting of the NDPSC, the old standard statements i, b, and d for naphthalene were replaced with new standard statements A, G1 and G3.

October 2003, NDPSC (#39)

At the October 2003 meeting of the NDPSC, the committee considered a proposal to vary the label of an existing registered product containing naphthalene for use as a moth repellent in wardrobes, clothes drawers and for the protection of books and other paper or cloth based material in storage. The committee agreed to defer with matter to the February 2004 meeting.

February 2004, NDPSC (#40)

In February 2004 the NDPSC considered naphthalene, including several case reports of naphthalene poisoning via differing exposure routes (mostly from overseas) and confirmed that the Schedule 6 entry was appropriate and that a new warning statement should be included in Appendix F, Part 1. This warning statement (105) was identical to the wording of the FAISD statement 44. The NDPSC concluded that this statement should be a requirement for naphthalene products to alert users to the potential hazard that naphthalene presents to young children.

June 2006, NDPSC (#47)

In 2006 the NDPSC again considered naphthalene in light of an Australian report of haemolytic anaemia in a child exposed to naphthalene. In this case, flakes had apparently been used in the storage of furniture, including the baby's cot. The NDPSC reconfirmed that the Schedule 6 entry was appropriate and that warning statement 105 should remain a requirement for naphthalene products to alert users to the potential hazard that naphthalene presents to young children.

ACCS Members recalled that Appendix F (Warning Statements and Safety Directions) no longer applied to agricultural and veterinary chemicals registered by the APVMA i.e. this was set entirely through the APVMA's product approach process, with the FAISD providing guidance on labelling for this process.

June 2011 Advisory Committee on Chemicals Scheduling (ACCS #2)

In June 2011, the ACCS considered a proposal to amend the Poisons Standard with respect to naphthalene. The applicant proposed to increase the restrictions on domestic use of naphthalene through scheduling, including (but not necessarily limited to) mothballs, blocks, discs, pellets or flakes. The ACCS recommended that the term "flake" be included in Poisons Standard Part 2 Labels and Containers paragraphs 17, 28 and 29. In addition to this, the ACCS recommended that the term "flake" be included in the Appendix F, Part 3 entries for camphor and naphthalene. The ACCS also recommended that the existing Schedule 6 naphthalene entry

be amended to exclude liquid hydrocarbons when present as impurities. The delegate agreed with the committee's advice and made a final decision with respect to naphthalene with an implementation date of 1 January 2012.

Australian regulations

Insecticide use of naphthalene is regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA), and products must comply with the APVMA's requirements, including labelling. There are nine (9) products containing naphthalene on the APVMA's PubCRIS.

Naphthalene is listed in Safe Work Australia's Hazardous Substances Information Systems (HSIS) as a Category 3 carcinogen with a risk phrase: "*R40 Limited evidence of a carcinogenic effect and as harmful by the oral route*".

International regulations

Reviews by the United States Environmental Protection Authority (US EPA) (2008), the Canadian Pest Management Regulatory Agency (PMRA) (2010) and the European Chemicals Bureau (2003) have not supported the use of loose or flaked forms of naphthalene.

European Union

Loose mothballs and flakes of naphthalene have not been available in the EU since mid-2009 when approval was withdrawn following a lack of commercial interest by manufacturers in funding new studies to support the chemical in a European review of biocide products.

Naphthalene is listed in Annex II/1167 "List of substances prohibited in cosmetic products' of the EU Regulation (EC) No 1223/2009.

Naphthalene is also considered a Class 2 Carcinogenic Substance.

United States of America (USA)

The US EPA does not permit the marketing of loose mothballs, thus requiring the containerisation of flakes and loose mothballs to reduce the risk of ingestion by children.

Canada

The PMRA has restricted naphthalene presentation to packaging that reduces the possibility for ingestion thus requiring the containerization of flakes and loose mothballs.

Naphthalene is in Schedule 5 and Schedule 7, Part 2 of the Export and Import of Hazardous Waste and Hazardous Recyclable Material Regulations SOR/2005-149.

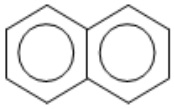
Naphthalene is also listed in the Ingredient Disclosure List SOR/88-64 of the *Hazardous Products Act* and must be included in the list of ingredients when present at concentrations greater than 1% w/w.

Substance summary

Naphthalene is a polycyclic aromatic hydrocarbon and white crystalline powder with a characteristic odour. It is used as a starting material for a variety of industrial chemicals, dyes, resins, solvents, lubricants and fuel components. Naphthalene is also a moth repellent and insecticide.

Naphthalene slowly sublimes under ambient conditions; the vapour repels moths but can also be inhaled by house occupants (characteristic mothball smell).

Table 1: Chemical information for naphthalene

Property	Naphthalene
CAS name	N/A
CAS number	91-20-3
Chemical structure	
Molecular formula	$C_{10}H_8$
Molecular weight	128.2 g/mol
IUPAC and/or common and/or other names	Bicyclo[4.4.0]deca-1,3,5,7,9-pentaene

Naphthalene is most commonly encountered by the public as mothballs or toilet deodorant blocks, but the compound is also generated from burning wood or tobacco and as a component of the essential oils of some medicinal and culinary herbs.

When used as a pest control product, naphthalene is an insecticide in the form of mothballs or flakes for control of moth and larvae which are destructive to textiles made of natural fibres. The products are placed in wardrobes, drawers, bedding stores, and similar areas where the naphthalene vapours can build up to levels toxic to the adult or larvae forms of the moth.

Cases of naphthalene poisoning in members of the public are regularly reported. The taste of naphthalene is not offensive to all people as children have been known to eat mothballs and toilet deodorant blocks, and case reports are available of pregnant women sucking on mothballs.

Metabolism

Following absorption into the liver, naphthalene is oxidised microsomal mixed-function oxidases to a range of metabolites, one or more of which are toxic. Following an initial 1, 2 epoxidation, naphthalene is converted to monohydric phenols such as 1- and 2-naphthols, dihydric phenols such as 1, 2- dihydroxynaphthalene and dihydrodiols such as dihydronaphthalene 1, 2-diol. These are mostly excreted as glucuronides or ethereal sulfates. Naphthalene 1,2-epoxide also reacts with reduced glutathione to form *S*-(2-hydroxy-l,2-dihydroxynaphthyl) glutathione. This in turn is converted to *S*- (hydroxy-l,2 dihydronaphthyl) acetyl-L-cystenine, which is excreted as I-naphthylmercapturic acid.

Toxicity

Ingestion or inhalation of naphthalene can lead to haemolytic anaemia which can be fatal. Inhalation, rat: LC50 = >340 mg/m^3/1H;

Oral, rat: LD50 = 490 mg/kg[2]

Pharmacology

Individuals with glucose-6-phosphate (G6P) deficiency are at increased risk when exposed to naphthalene.

G6P deficiency is reportedly present in about five per cent of Australians, mainly those of Asian, African, Middle Eastern or Mediterranean descent. This enzyme deficiency makes affected individuals liable to red cell haemolysis following naphthalene exposure. Haemolysis, whether due to chemical exposure or underlying pathological processes, leads to the production of bilirubin (as a breakdown product of haemoglobin from the lysed red cells) which causes jaundice. In adults and older children, jaundice is relatively harmless in itself. However, if this process occurs in the fetus or infant when the blood brain barrier is not fully formed, some of this bilirubin enters the brain and is deposited in cell bodies (grey matter), especially the basal ganglia, causing irreversible damage. Depending on the level of exposure, the effects range from clinically unnoticeable to severe brain damage and even death. In severe cases of haemolysis there can also be serious kidney and liver damage resulting from precipitated haemoglobin.

Human carcinogenicity

The International Agency for Research on Cancer[18] concluded that "there is inadequate evidence in humans for the carcinogenicity of naphthalene. There is sufficient evidence in experimental animals for the carcinogenicity of naphthalene.

The overall evaluation is that naphthalene is possibly carcinogenic to humans (Group 2B). Whilst the evidence for carcinogenicity in rodents is convincing, the relevance to humans at likely domestic exposure levels is questionable as the available evidence points to a considerably lower susceptibility of humans than of rodents.

Tumours in rodents occurred in tissues especially prone to naphthalene injury (hyperplasia, inflammation and/or necrosis) when exposure was by either the inhalation or the intraperitoneal route.

Pre-meeting public submissions

Four public submissions were received before the first closing date in response to an invitation published on 31 August 2018 under regulation 42ZCZK of the Regulations; one in support of the proposal and three opposed.

The main points provided in opposition of the amendment were:

- Naphthalene toxicity is well established and severe toxicity can occur from relatively small oral or inhaled exposures. Those in the population with G6PD deficiency are at particular risk, and are usually not aware of this increased individual risk.
- The NSW Poisons Information Centre receives calls regarding exposures to naphthalene (92 calls since 2014, 32 requiring hospitalisation) as well as exposures to moth balls of an unknown content, potentially containing naphthalene (113 calls since 2014, 16 requiring hospitalisation). Many of these phone calls involve loose moth balls or parts of moth balls which had escaped the caged packaging designed to prevent exposures.
- With the ready availability of safer alternatives, the risk benefit analysis of naphthalene now favours a change to Schedule 7.

[18] IARC (2002); http://www.inchem.org/documents/iarc/vol82/82-06.html

The main points provided in support of the amendment were:

- The proposal to limit public exposure of naphthalene only addresses the safety of mothballs in the domestic setting. Naphthalene is much more predominantly used in Australia, in industrial products and processes i.e. as a solvent, in dyes, heat transfer fluid, additives, coatings, textiles, binders, adhesives and surfactants. It is also an impurity in liquid hydrocarbons such as diesel (hence the current exemption).
- Naphthalene is found in naphtha and distillate fractions and can be present in reasonable quantities in aromatic solvents. With the proposed scheduling amendment, a number of automotive and agricultural products would become Schedule 7 Poisons.
- Adding all forms and uses of naphthalene to Schedule 7 as proposed would present significant issues for industry. It would mean that industrial products consisting of and/or containing naphthalene (other than liquid hydrocarbons where it is present as an impurity) would be inadvertently captured and required to comply with the Schedule 7 requirements, including licensing. It would become extremely difficult, if not impossible to continue marketing these products. This seems a disproportionate effect given that no public health concerns have been raised with these industrial uses of naphthalene and naphthalene containing products.
- There is lack of clarity as to whether or not naphthalene occurring naturally in petroleum crude oil would or would not be considered to be an impurity. Previous requests for clarification from the Scheduling Secretariat have produced advice that 'this would constitute a legal opinion and cannot be given.' With the Appendix G exclusion concentration of 1 mg per litre or kilogram it could cause undue concern and hardship to Industry.
- The current Schedule 6 exception on hydrocarbon liquids for naphthalene could be improved as the term 'impurity' causes confusion with the general cut-off limits (10 mg/kg) allocated for S6.
- Suggested changes to the proposed S7 entry (if warranted) and (two alternative) changes to S6;

  Schedule 6 NAPHTHALENE (excluding its derivatives) except:

  (a) when present at less than 0.5% naphthalene in liquid hydrocarbons.

  (b) when included in Schedule 7; or

  (c) when in liquid hydrocarbons ~~as an impurity~~; or

  (d) when included in Schedule 7

  Schedule 7 - New Entry

  NAPHTHALENE in mothball use

Joint ACMS-ACCS advice

The committee recommended that a new schedule 10 Poisons Standard entry be created for naphthalene as follows:

Schedule 10 – New Entry

NAPHTHALENE for domestic use **except** when enclosed in a device which, in normal use, prevents removal or ingestion of its contents.

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NAPHTHALENE

Schedule 6

Schedule 10

Appendix E, Part 2

Appendix F, Part 3

Appendix G

In addition, the committee recommended an **implementation date of 1 June 2019**, since non-compliant products pose a serious risk to the public, and this is the earliest date possible.

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

The reasons for the advice included:

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

- The benefit of use of naphthalene rather than camphor mothballs is not clear, and there is increased risk. However, the risk is significantly mitigated if proper containment is used.
- Known risk of toxicity in domestic environment due to inhalation and ingestion, notably in children.
- Continued reports of toxicity indicate current scheduling, labelling and packaging restrictions may be ineffective.
- Known benefits in industrial products and processes.

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

- Domestic use as moth repellent; safer alternatives available.
- 5/9 of the APVMA registered products are moth ball products for home use, the others are insecticides.
- Predominant use in industrial products and processes.

(c) the toxicity of a substance:

- Toxicity appears to meet the SPF for Schedule 6. However:
    - Dangerous poison; ingestion or inhalation can lead to haemolytic anaemia which can be fatal.
    - 100 mg can be fatal in a child; as little as one mothball (can contain 0.5-5 g naphthalene) can result in toxicity in children.
    - EPA has classified naphthalene as a Group C, possible human carcinogen.

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

- Approved products are contained and therefore reduce risk. Loose naphthalene balls and flake for domestic use are not legal products, but may be singled out for special scheduling controls.
- Packaging requirements - naphthalene in ball, block, disc, pellet or flake form for domestic use must be enclosed in a device which prevents removal or ingestion of its contents, is incapable of reacting with the poison, is sufficiently strong, has the word "POISON" and the name of the poison embossed or indelibly printed on it.
- Evidence these requirements are not being complied with in all cases, availability in some retail outlets and online in loose form.

(e) the potential for abuse of a substance:

- Some reports of abuse via deliberate inhalation of mothballs.

3. Advisory Committee on Chemicals Scheduling (ACCS #23)

3.1 2-chloro-p-phenylenediamine

Delegate's interim decision

Interim decision:

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

Schedule 6 – Amend Entry

PHENYLENEDIAMINES including alkylated, arylated, halogenated and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

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

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

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

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

written in letters not less than 1.5 mm in height.

Schedule 10 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Appendix E Part 2 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Standard statements when used in hair dyes:

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

- Standard statements when used in preparations other than hair dyes:
  - **A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)];
  - **G1** (Urgent hospital treatment is likely to be needed; Note - the words 'at once' to be added to instruction A);
  - **G3** (If swallowed, do NOT induce vomiting);
  - **E1** (If in eyes wash out immediately with water); and
  - **S1** (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F Part 3 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Warning statements when used in hair dyes:
  - **21** WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
- Warning statements when used in in preparations other than hair dyes:
  - **28** (Over) (Repeated) exposure may cause sensitisation.
- Safety directions when used in preparations other than hair dyes:
  - **1** (Avoid contact with eyes);
  - **4** (Avoid contact with skin); and
  - **8** (Avoid breathing dust (or) vapour (or) spray mist).

Index – Amend entry

PHENYLENEDIAMINES cross reference: ALKYLATED, ARYLATED, HALOGENATED and NITRO- PHENYLENEDIAMINES, DIETHYL-PARA-PHENYLENEDIAMINE, DIMETHYL-PARA-PHENYLENEDIAMINE

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Proposed date of effect of the proposed amendment: **1 June 2019**

Reasons for interim decision:

The reasons for the interim decision are as follows:

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

2-chlorophenylenediame and its sulfate are strong skin sensitisers and there is evidence of severe allergic reactions when used in humans as a dye for eyebrows and eyelashes, with symptoms of itchy dermatitis on eyebrows, itchy dermatitis on the eye lids and swollen eyelids, watering, itchiness and redness in both eyes, followed by severe inflammation of eye lids and conjunctival chemosis reported.

Similar to other phenylenediamine derivatives, the potential for skin sensitisation clearly presents a risk when the chemicals are used in cosmetic products for dyeing hair, eyebrows and eyelashes. However, the risks can be managed by the imposition of concentration restrictions and appropriate label warning statements, as have previously been applied to other sensitising phenylenediamine derivatives in the Poison Standard when used in hair, eyebrows and eyelashes dyeing products.

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

Internationally, 2-chloro-p-phenylenediamine and its sulfate are used in cosmetics, hair dyes and eyelash and eyebrow tints. The free base, 2-chloro-p-phenylenediamine is used in oxidative hair dye formulations at concentrations up to 4.6% and for dyeing eyelashes and brows. Prior to use it is mixed with 3% hydrogen peroxide solution in a ratio 1:1. The free base phenylenediamine is reported to also have domestic and industrial uses.

Although these chemicals are not reported to be used in Australia, there is a potential for public exposure through products imported from overseas.

c. the toxicity of a substance:

The halogenated derivatives are skin sensitisers and exhibit toxicities consistent with other members of the schedule entry. They are acutely toxic via oral, dermal and inhalation routes, are strong sensitisers and eye irritants. Based on available data, the chemicals are not expected to be genotoxic, carcinogenic or have developmental toxicity.

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

The Schedule 6, Appendix E, Part 2 and Appendix F, Part 3 entries for phenylenediames in the Poisons Standard, covers and includes specifies labelling requirements, when used in hair dyes and eyelash and eyebrow tinting products. The immediate containers and primary packs of these products must be labelled with the appropriate warning statements, safety directions and first aid instructions to manage potential adverse effects associated with their use.

e. the potential for abuse of a substance:

Non-adherence to hair dye and eyebrow and eyelash tinting product label warning statements, safety directions and first aid instructions by consumers could potentially lead to adverse health effects, which could be exacerbated by repeat applications.

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

The EU Scientific Committee on Consumer Safety (SCCS) concluded that the use of 2-chloro-p-phenylenediamine and its sulfate for dyeing hair, eyelashes and eyebrows is not safe for the consumer (2013). This recommendation was made primarily due to the inability to calculate margins of safety for use in oxidative hair dye formulations for eyebrows and eyelashes for a maximum use concentration of 4.6%. In 2018 the SCCS extended its opinion and conclusions to the use of these chemicals in products used for dyeing hair on the head to reflect the greater

surface area of skin in contact with the chemical with this use pattern. Consequently, the European Parliament made the decision to include 2-chloro-p-phenylenediamine, its sulfate and dihydrochloric salts, when used as substances in hair dye products, including eyebrow dye products and eyelash products, in the list of prohibited substances in Annex II to Regulation No 1223/2009 of the European Parliament and of the Council on cosmetic products.

Overall conclusions

Having considered all the relevant information, the weight of evidence indicates that the toxicological profile of 2-chloro-p-phenylenediamine and its sulfate and, their potential for skin sensitisation is similar to other phenylenediamine derivatives when used in hair dye and eyelash and eyebrow tinting products.

Including 2-chloro-p-phenylenediamine and its sulfate as halogenated derivatives of pheneyenediames in existing scheduled entries, risks associated with their use can be managed by the existing regulatory controls imposed by the Poisons Standard. Further, inclusion of 2-chloro-p-phenylenediame and its sulfate as halogenated derivatives of pheneyenediames in the existing scheduling entries will provide clarity and confirmation to industry that these chemicals are captured by the existing scheduling entries for phenylenediamines and will not result in any significant regulatory impact upon them.

Materials considered

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

- The application to amend the current Poisons Standard with respect to naphthalene;
- The public submissions received before the first closing date;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #20);
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal for 2-chloro-p-phenylenedaime was published on the TGA website on 31 August 2018 at Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2018.

Background information for solvent yellow

Delegate's referral to ACCS

An application was submitted by National Industrial Chemicals Notification and Assessment Scheme (NICNAS), as part of its Inventory Multi-tiered Assessment and Prioritisation (IMAP) program to amend the Poisons Standard with respect to the group entry for Phenylenediamines. The application proposes to amend the existing Schedule 6 and Schedule 10 group entries for Phenylenediamines in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) to include the halogenated derivatives, 2-chloro-p-phenylenediamine and its sulfate.

Applicant's scheduling proposal and reasons

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

Schedule 6 – Amend Entry

PHENYLENEDIAMINES including alkylated, arylated, halogenated and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

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

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

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

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

written in letters not less than 1.5 mm in height.

Schedule 10 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows except when included in Schedule 6.

Appendix E Part 2 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Standard statements when used in hair dyes:
  - **A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)]
  - **E1** (If in eyes wash out immediately with water).
- Standard statements when used in preparations other than hair dyes:
  - **A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)];
  - **G1** (Urgent hospital treatment is likely to be needed; Note - the words 'at once' to be added to instruction A);

- **G3** (If swallowed, do NOT induce vomiting);
- **E1** (If in eyes wash out immediately with water); and
- **S1** (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F Part 3 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Warning statements when used in hair dyes:
  - **21** WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
- Warning statements when used in in preparations other than hair dyes:
  - **28** (Over) (Repeated) exposure may cause sensitisation.
- Safety directions when used in preparations other than hair dyes:
  - **1** (Avoid contact with eyes);
  - **4** (Avoid contact with skin); and
  - **8** (Avoid breathing dust (or) vapour (or) spray mist).

The applicant's reasons for the proposal are:

- the chemical and its sulfate is reported to have international use in cosmetics for dyeing hair, eyebrows and eyelashes, and in domestic products. It is expected they are used in similar products in Australia;
- the chemicals are strong skin sensitisers;
- there is evidence of severe allergic reactions in humans when 2-chloro-p-phenylenediamine is used to dye eyebrows and eyelashes; and
- the chemicals are acutely toxic following oral exposure.
- similar to other phenylenediamine derivatives, the potential for skin sensitisation clearly presents a risk when the chemicals are used in cosmetic products for dyeing hair, eyebrows and eyelashes. This risk can be controlled by imposition of concentration restrictions and warning labels, as have previously been applied to other sensitising phenylenediamine derivatives in the SUSMP for use in hair, eyebrows and eyelashes dyeing products.

Current scheduling status

2-chloro-p-phenylenediamine/2-chloro-p-phenylenediamine sulfate are not currently scheduled in the current Poisons Standard.

Phenylenediamines are listed in the Poisons Standard as follows:

Schedule 6

PHENYLENEDIAMINES including alkylated, arylated, and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

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

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

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

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

written in letters not less than 1.5 mm in height.

Schedule 10

PHENYLENEDIAMINES, including alkylated, arylated, and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows except when included in Schedule 6.

Scheduling history

2-chloro-p-phenylenediamine/2-chloro-p-phenylenediamine sulfate are not specifically scheduled and has not been previously considered for scheduling; therefore a scheduling history is not available.

In January 1955, the Committee on Poisons Schedule decided to list phenylene toluene and other alkylated benzene diamines in Schedule 2. At that time Schedule 2 substances were considered to be Poisons, the sale of which was restricted to certain specified categories of vendors and which were subject to identical packing and labelling requirements to those of Schedule 1 but which were not required to be entered in a Poisons Register.

In March 1980, the Poisons Schedule Committee (PSC) decided to delete the Schedule 6 aromatic amines entry and amend the Schedule 6 phenylene diamines entry to include alkylated phenylene diamines.

In May 1985, the PSC noted that a number of phenylene diamines in Schedule 6 listing were individually listed as well as being included in the general entry for phenylene diamines. The PSC agreed that the individual entries were not required in addition to the general entry for phenylene diamines and decided to delete the individual entries. The PSC agreed that no change was required to the Schedule 2 phenylene diamines entry.

In August 2000, the NDPSC agreed to exempt hair dye products containing phenylenediamines or toluenediamines from scheduling, conditional upon specified labelling.

In February and June 2004, the NDPSC considered the outcomes of investigations into incorrectly packed and labelled eyelash/brow tints containing

phenylenediamines/toluenediamine and in October 2004, the NDPSC agreed to foreshadow amendments to prohibit use for eyelash/brow tinting. This proposal was varied by the February 2005 NDPSC meeting which instead agreed to foreshadow two options: to allow either salon use only, or all domestic use, of these eyelash/brow tints as Schedule 6 products (when compliant with the specified labelling).

In June 2005, the NDPSC concluded that the potential risk of causing a strong allergic response in a small number of individuals could be minimised through appropriate labelling. The NDPSC therefore agreed to that eyelash/brow tints were Schedule 6 poisons when appropriately labelled.

In June 2006, the NDPSC considered a request for flexibility in applying the mandatory labelling for eyelash/brow tints containing phenylenediamine and toluenediamine. The NDPSC indicated that, as the main risk was sensitisation, which in this case did not demonstrate a clear dose response, strong label warnings were required before such products could be available as Schedule 6. As there was a risk of separation of an outer pack from the immediate container, it was appropriate that all mandatory labelling continued to be applied to the immediate container, regardless of pack size. That the Schedule 6 warning statement would need to be applied, whether the use was domestic or industrial, or the product would default to Appendix C. The NDPSC further confirmed that the introduction to both Appendix E and F provided sufficient flexibility to allow for variation of product use and formulation.

In February 2007, the NDPSC considered the labelling requirements for single use composite pack hair preparations, including those containing phenylenediamines or toluenediamine, in view of amending various references to 'hair dyes' to 'hair preparations'. The NDPSC decided not to amend these references as there was potential for inadvertent capture of products for non-dying use patterns.

In February 2008, the NDPSC considered the scheduling of phenylenediamine and toluenediamine in eyelash/brow tints including restrict non-professional supply to ≤ 5 mL and limit non-professional supply to 'complete kit' forms (i.e. all reagents). The NDPSC agreed that it was not appropriate to address separate supply of a developer for eyelash/brow tinting through the scheduling process as there was little evidence of an actual public health risk from products not being sold in 'complete kit' form. The NDPSC also agreed that there was little evidence to support a pack size restriction on the availability of eyelash/brow tints containing phenylenediamine / toluenediamine.

Australian regulations

2-chloro-p-phenylenediamine (CAS 615-66-7) and 2-chloro-p-phenylenediamine sulfate (CAS 6219-71-2) are present on the Australian Inventory of Chemical Substances (AICS).

2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are not listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 5 of 2017.

2-chloro-p-phenylenediamine and 2-chloro-p-phenylenediamine sulfate are not excipients or active ingredients in any medicine on the Australian Register of Therapeutic Goods (ARTG).

International regulations

The chemicals in this group have the following international restrictions (Galleria Chemica):

- The New Zealand Inventory of Chemicals (NZIoC) allows for possible use as a component in a product covered by a group standard but is not approved for use as a chemical in its own right.
- 2-chloro-p-phenylenediamine was registered under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as of 17 August 2016. The registration dossier was

updated on 5 July 2018, following compliance checks by the European Chemicals Agency (ECHA).

- 2-chloro-p-phenylenediamine sulfate was registered under REACH as of 9 January 2018.

The chemicals in this group are listed as hair dyes in the European Commission (EU) Cosmetic Ingredients and Substances (CosIng) database, and as hair colourants in the United States (US) Personal Care Product Council International Cosmetic Ingredients (INCI) Directory.

The free base (CAS No. 615-66-7) is used in oxidative hair dye formulations at concentrations up to 4.6% and for dyeing eyebrows and eyelashes, mixed with 3% hydrogen peroxide solution in a 1:1 ratio prior to use in both applications (SCCS, 2013). The sulfate salt (CAS No. 6219-71-2) is used in hair dyes at concentrations up to 2% (before dilution) (CIR, 2011).

Other international uses have been identified for the chemicals through the US Department of Health and Human Services Household Products Database (US HPD) and the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers.

The free base has reported domestic use in the following:

- anti-bacterial hand wash.

The free base has reported non-industrial use in the following:

- weed killer/pesticides; and
- pharmaceuticals.

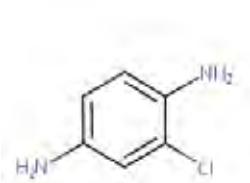
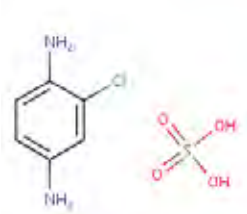
The free base is not commercially produced in the US (US National Library of Medicine's Hazardous Substances Data Bank (HSDB)). The sulfate salt seems to have limited use in the US with the Compilation of Ingredients Used in Cosmetics in the US (CIUCUS), 2011 listing the sulfate salt in only one product.

The Scientific Committee on Consumer Products (SCCP) concluded that it is of the opinion that the use of 2-chloro-p-phenylenediamine (CAS No. 615-66-7) for dyeing hair, eyelashes and eyebrows is not safe for the consumer (SCCS, 2013). However, this recommendation was made primarily due to the inability to calculate margin of safety for use in oxidative hair dye formulations for eyebrows and eyelashes for a maximum use concentration of 4.6%. This does not preclude the scheduling changes proposed for the chemical and its sulfate to manage skin sensitisation risk.

Substance summary

Table 1: Chemical information for 2-chloro-p-phenylenediamine

Element	2-chloro-p-phenylenediamine /2-chloro-p-phenylenediamine sulfate	
CAS name	1,4-benzenediamine, 2-chloro-	1,4-benzenediamine, 2-chloro-, sulfate
CAS Number	615-66-7	6219-71-2

Chemical structure		
Molecular formula	$C_6H_7ClN_2$	$C_6H_7ClN_2.xH_2O_4S$
Molecular weight	140.60 g/mol	240.70 g/mol
IUPAC and/or common and/or other names	2-chloro-p-phenylenediamine (INCI) 2-chlorobenzene-1,4-diamine (IUPAC) 3-chloro-4-aminoaniline; Ursol Brown O; C.I. 76065	2-chloro-p-phenylenediamine sulfate (INCI) 2-chlorobenzene-1,4-diammonium sulfate (IUPAC) C.I. 76066; C.I. Oxidation Base 13A; Rodol Brown SO

As the toxicokinetics and toxicity of the phenylenediamine derivative (free base; CAS No. 615-66-7) and its sulfate salt (CAS No. 6219-71-2) are expected to be similar, they have been grouped together for purposes of the human health risk assessment. While there may be differences between the sulfate salt and the free base with respect to local effects, the speciation of the chemicals in biological fluids will be dependent on pH but independent of the original chemical form (SCCS, 2013).

Table 2: Acute toxicity end-points for 2-chloro-p-phenylenediamine

Toxicity	Species	2-chloro-1,4-benzenediamine	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	729-1190 mg/kg bw	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	-	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	-	No data	N/A
Skin irritation	Rabbit	Not irritating	N/A
Eye irritation	Rabbit	Slight-moderately irritating	Schedule 5
Skin sensitisation (non-guideline guinea pig test)	Guinea pig	Skin sensitising	Schedule 6

Acute toxicity

The chemicals in this group are considered to have moderate acute toxicity following oral exposure with a median lethal dose (LD_{50}) between 729-1190 mg/kg bw based on data available on 2-chloro-p-phenylenediamine.

Irritation

Based on available data, 2-chloro-p-phenylenediamine is not irritating to skin under the test conditions. No data are available for the sulfate salt. However, since the local irritation effects of the salt are not expected to be greater than those of the free base, the sulfate salt is not likely to be irritating to skin based on data available for the free base.

Sensitisation

The chemicals in this group are considered to be sensitising to skin based on data available on 2-chloro-p-phenylenediamine.

In a non-guideline test, 2-chloro-p-phenylenediamine was reported to be a strong sensitiser producing a reaction in 9 out of 15 guinea pigs within 24 hours of challenge (SCCS, 2013). Although the test was described as 'Magnusson-Kligman protocol' (SCCS, 2013), study details showed that it was not a guinea pig maximisation test (GPMT). Female Pirbright white guinea pigs (n=10–15/group) were intracutaneously induced with the chemical at 3% for 5 consecutive days. After 4 weeks of induction, the animals were challenged with topical application of the chemical at up to 0.3%. Use of Freund's Complete Adjuvant (FCA) is not mentioned.

Quantitative structure-activity relationship (QSAR) modelling using OECD QSAR Toolbox showed protein binding alerts for 2-chloro-p-phenylenediamine and its metabolites for skin sensitisation. One QSAR modelling study based on local lymph node assay (LLNA) data and topological substructural molecular descriptors (TOPS-MODE) predicted a sensitisation potency of 1.6 for the free base (close to p-phenylenediamine with a predicted score of 1.8), identifying 2-chloro-p-phenylenediamine as a strong/moderate sensitiser (Søsted et al., 2004).

Repeat-dose toxicity

The chemicals in this group are not expected to cause serious damage to health following repeated oral exposure at low doses based on available data.

Mutagenicity / Genotoxicity

The chemicals in this group are not expected to be genotoxic based on available data. Although 2-chloro-p-phenylenediamine tested positive for gene mutations in vitro, it was negative for genotoxicity in vivo. Furthermore, read-across data on 1,4-benzenediamine (CAS No. 106-50-3) and its analogues indicate that the chemicals in this group are not likely to be genotoxic.

Carcinogenicity

The chemicals are not expected to be carcinogenic based on available data.

Reproduction and developmental toxicity

The chemicals in this group are not expected to have specific developmental toxicity based on the limited data available on 2-chloro-p-phenylenediamine. No data is available for reproductive toxicity.

Observation in humans

The following three individual case reports give evidence of severe allergic reactions/contact dermatitis produced within 24 hours of dyeing eyelashes and eyebrows with a dye containing 2-chloro-p-phenylenediamine:

- itchy dermatitis on eyebrows;
- itchy dermatitis on eye lids; and
- swollen eyelids, watering, itchiness and redness in both eyes, followed by severe inflammation of eye lids and conjunctival chemosis (swelling).

Public exposure

Since the expected use of the chemicals in Australia is in cosmetic products for dyeing hair, eyebrows and eyelashes, the main route of public exposure is expected to be through the skin.

Pre-meeting public submissions

One public submission, which was supportive of the scheduling proposal, was received before the first closing date in response to an invitation published on 31 August 2018 under regulation 42ZCZK of the Regulations.

The main points provided in support of the amendment were:

- The proposal provides clarification and confirmation that halogenated derivatives of the entries for phenylenediamines are captured by the existing scheduling entries.
- The proposal is not expected to result in any significant regulatory impact.

ACCS advice

The committee recommends that the current Schedule 6 entry and Schedule 10 entries for PHENYLENEDIAMINES be amended as follows:

Schedule 6 – Amend Entry

PHENYLENEDIAMINES including alkylated, arylated, halogenated and nitro derivatives not elsewhere specified in these Schedules:

a) in preparations packed and labelled for photographic purposes;

b) in preparations packed and labelled for testing water except tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, "Do not discard testing solutions into the pool";

c) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

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

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

d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

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

written in letters not less than 1.5 mm in height.

Schedule 10 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives, in preparations for skin colouration, tattooing and dyeing of eyelashes or eyebrows except when included in Schedule 6.

Appendix E Part 2 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Standard statements when used in hair dyes:
  - **A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)]
  - **E1** (If in eyes wash out immediately with water).
- Standard statements when used in preparations other than hair dyes:
  - **A** [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)];
  - **G1** (Urgent hospital treatment is likely to be needed; Note - the words 'at once' to be added to instruction A);
  - **G3** (If swallowed, do NOT induce vomiting);
  - **E1** (If in eyes wash out immediately with water); and
  - **S1** (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F Part 3 – Amend Entry

PHENYLENEDIAMINES, including alkylated, arylated, halogenated and nitro derivatives

- Warning statements when used in hair dyes:
  - **21** WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
- Warning statements when used in in preparations other than hair dyes:
  - **28** (Over) (Repeated) exposure may cause sensitisation.
- Safety directions when used in preparations other than hair dyes:
  - **1** (Avoid contact with eyes);
  - **4** (Avoid contact with skin); and

- **8** (Avoid breathing dust (or) vapour (or) spray mist).

Index – Amend entry

PHENYLENEDIAMINES cross reference: ALKYLATED, ARYLATED, HALOGENATED and NITRO- PHENYLENEDIAMINES, DIETHYL-PARA-PHENYLENEDIAMINE, DIMETHYL-PARA-PHENYLENEDIAMINE

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The committee also recommended an implementation date of **1 June 2018**.

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

The reasons for the advice included:

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

- Strong sensitisers and evidence in humans of severe allergic reactions when used as a dye for eyebrow and eyelashes.

  Management of risk through appropriate concentration restrictions and labelling.

- The critical health effects for risk characterisation include:
  - local effects- eye irritation and skin sensitization; and
  - systemic acute effects- acute toxicity by oral, dermal and inhalation routes.

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

- Not reported to be used in Australia.
- Internationally used in cosmetics, hair dyes and dye for eyelash and eyebrow tints.
- The chemicals are primarily used in cosmetics. 2-chloro-p-phenylenediamine (CAS No. 615-66-7) is reported to also have domestic and industrial use.

(c) the toxicity of a substance:

- Skin sensitiser.
- The halogenated derivatives exhibit toxicities consistent with other members of the schedule entry.

(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

- Draft Amendment to EU Regulations inclusion of 2-Chloro-p-Phenylenediamine and sulfate and dihydrochloride salts to prohibited substances.