



Australian Government

Department of Health
Therapeutic Goods Administration

Publication of interim decisions proposing to amend, or not amend, the current Poisons Standard, September 2018

10 September 2018

Publication of interim decisions made pursuant to regulations 42ZCZN of the Therapeutic Goods Regulations 1990

In accordance with regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the Regulations), this notice gives effect to the Secretary's obligation to publish 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 June 2018 meeting of the Advisory Committee on Medicines Scheduling (ACMS #24); and
- proposed amendments referred to the June 2018 meeting of the Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS #19).

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 **11 October 2018** (second closing date).

See [How to respond](#) below.

How to respond

Your submission should:

- be relevant to the proposed amendment, 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. (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 \(docx,65kb\)](#).

Submissions might also include:

- Suggested improvements to the proposed amendment; 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 web page 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 \(docx,65kb\)](#)
- 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 web page titled [Scheduling delegates' final decisions](#) on **29 November 2018**.

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 public 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, please go to the TGA's webpage on [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).

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

1.1 Sildenafil

Delegate's interim decision

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

Reasons for interim decision

The reasons for the interim decision are as follows:

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

- Sildenafil does not satisfactorily meet the following Schedule 3 SPF criteria:¹
 - § The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately. The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use.

This is because:

- § Erectile Dysfunction (ED) is a symptom with an underlying cause which should be diagnosed before treatment.
- § The use of the sildenafil at established therapeutic dosage levels may mask the symptoms or delay diagnosis of cardiovascular disease (CVD). ED is an independent risk factor for CVD.²
- § CVD cannot be diagnosed by a pharmacist. The list of diagnosis tools (including ECG and other cardiac testing) recommended by the Princeton III Consensus Recommendations for the Management of ED and CVD are not possible in a pharmacy setting.³
- § As well the Andrology Australia Clinical Summary Guide on Erectile Dysfunction⁴ outlines the history, examination requirements and investigations for diagnosing ED of which a number are only possible by or accessible through a medical practitioner.
- Sildenafil meets the following Schedule 4 SPF criteria:¹
 - § The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention. Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.

This is because:

¹ The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018)

² Uddin SM, Mirbolouk M, Dardari Z et al. Erectile dysfunction as an independent predictor of future cardiovascular events: the multi-ethnic study of atherosclerosis. *Circulation* 2018;June 11;[Epub ahead of print]

³ Nehra et al. (2012) 'The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease', *Mayo Clin Proc*, 87(8), 766-778

⁴ Andrology Australia Clinical Summary guide 9 – Erectile dysfunction – Diagnosis and Management Update March 2018 found at <https://andrologyaustralia.org/wp-content/uploads/clinical-summary-guide-09.pdf> (Accessed 25 July 2018)

§ The list of diagnosis tools (including ECG and other cardiac testing) recommended by the Princeton III Consensus Recommendations for the Management of ED and CVD are not possible in a pharmacy setting and require medical intervention.⁵

§ As well the Andrology Australia Clinical Summary Guide on Erectile Dysfunction⁶ outlines the history, examination requirements and investigations for diagnosing ED of which a number are only possible by or accessible through a medical practitioner.

§ One of the causes of ED is CVD, a medical condition that requires medical intervention through diagnosis, management and monitoring.

- Without medical diagnosis of the cause of the ED and of any potentially underlying serious medical conditions (such as CVD and diabetes) the risks associated with self-treatment of ED outweigh the benefits of improved consumer access to sildenafil through availability from a pharmacist.
- There is no evidence that patients will consult with their general practitioner (GP) on the advice of their pharmacist.⁷
- There is no evidence that the benefits of improved access for consumers are greatly outweighed by the risk of improper diagnosis or treatment of ED or associated risk factors by a pharmacist.

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

- ED is a symptom the potential causes of which cannot be diagnosed by the patient or pharmacist. The risk of facilitating ED treatment without appropriate diagnosis or treatment of any underlying serious medical conditions is too great to recommend sildenafil be moved to Schedule 3.
- Sildenafil is for the treatment of the symptom but does not treat the underlying cause.

(c) the toxicity of a substance:

- Although sildenafil has well known side-effects and drug interactions, the risk of facilitating ED treatment without appropriate diagnosis or treatment of any underlying serious medical conditions is too great to recommend sildenafil be moved to Schedule 3.
- Risk of hypotension.
- Sildenafil has a significant adverse effect profile that requires medical monitoring.
- Drug-drug interactions may potentiate sildenafil toxicity.

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

- Limited pack size is considered to not appropriately address risk of harms to consumers brought about by a lack of medical oversight in diagnosing the cause of ED before supply of sildenafil.

⁵ Nehra et al. (2012) 'The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease', *Mayo Clin Proc*, 87(8), 766-778

⁶ Andrology Australia Clinical Summary guide 9 – Erectile dysfunction – Diagnosis and Management Update March 2018 found at <https://andrologyaustralia.org/wp-content/uploads/clinical-summary-guide-09.pdf> (Accessed 25 July 2018)

⁷ Morales AM, Hatzichristou D, Lladós JM et al. Community pharmacy detection of erectile dysfunction in men with risk factors or who seek treatment or advice but lack a valid prescription. *J Sex Med* 2013;10:2303-2311

(e) the potential for abuse of a substance:

- Misuse by men without erectile dysfunction is already known to occur, including in combination with illicit drugs such as MDMA (3,4-methylenedioxymethamphetamine).
- Issues with counterfeit sildenafil are recognised, however increasing consumer access to sildenafil through down scheduling is not considered an appropriate mechanism to address this problem.

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

- Educational campaigns to raise awareness of the association between erectile dysfunction and serious medical conditions and to direct men to discuss problems relating to their sexual function with their GP can be undertaken, without requiring sildenafil to be down scheduled.
- Overcoming stigma with ED and improving treatment rates would be better addressed through consumer education and information.
- It is not believed that consumers are more likely to speak to their pharmacist about ED rather than their GP.
- No new relevant evidence supporting the down scheduling to Schedule 3 was provided in the applicant's submission. There was no evidence provided by the applicant on the New Zealand (NZ) experience of having sildenafil available from pharmacists despite it having been available since 2014.
- A recent publication on the NZ pharmacists experience⁸, although only involving 35 pharmacists, concluded that "New Zealand's model of pharmacist supply of sildenafil appears workable with some areas for improvement identified". However it was noted that "Many men requesting supply fell outside of the parameters, resulting in medical referral." It noted that "Many pharmacists estimated that over half (range 10–80%) of new requests for sildenafil resulted in medical referral without supply, commonly because of smoking, age over 70 years, or elevated blood pressure, occasionally diabetes and multiple medications were mentioned."
- There was no proposed Appendix M education or checklist material included in the application so until this is provided, it is difficult to assess whether an Appendix M listing would mitigate the risks of down scheduling. An appendix M listing would need to address:
 - § Development of accredited competency-based training for pharmacists by an appropriate accredited training body.
 - § Requirements for pharmacists to have written documentation of their consultation, outlining the clinical assessment they undertook and whether they supplied medication or referred.
 - § Well-developed clinical referral pathways for pharmacists that must be adhered to.
- Appendix M is not appropriate for ED and sildenafil treatment given that ED is a symptom of other conditions which require medical practitioner diagnosis, monitoring and treatment.

⁸ Braund R *et al.* Pharmacist supply of sildenafil: pharmacists' experiences and perceptions on training and tools for supply. *Int J Clin Pharm.* 2018 Jun;40(3):650-658.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to sildenafil;
- The applicant's presentation to the Advisory Committee on Medicines Scheduling;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- 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; and (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 was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for sildenafil

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to sildenafil. The application proposed to create new Schedule 3, Appendix H and Appendix M entries for sildenafil and to amend the Schedule 4 entry.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 3 – New Entry

SILDENAFIL in divided preparations for oral use containing 50 mg of sildenafil per dosage unit in packs of not more than 8 dosage units when compliant with the requirements of Appendix M.

Schedule 4 – Amend Entry

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

Appendix H – New Entry

SILDENAFIL.

Appendix M – New Entry

SILDENAFIL.

Supply of Schedule 3 sildenafil will be contingent on:

- § the sponsor making Continuing Professional Development (CPD) accredited training available to pharmacists; and
- § the sponsor providing a patient assessment tool to facilitate screening and counselling by the pharmacist.

The applicant's reasons for the proposal were:

- The proposal has been submitted to make sildenafil 50 mg available over the counter (OTC) without a prescription accompanied with appropriate informative consumer and pharmacist educational programmes and Schedule 3 advertising. The proposal will help reach men with erectile dysfunction (ED) who do not seek help from their doctor about their condition. It will also direct men away from the unregulated supply of imported ED medicines.
- The proposal will provide a safer alternative route for genuine, clinically effective and high quality treatment and advice for those men already using or contemplating using unregulated internet sources of sildenafil 50 mg. It will also help destigmatise ED, raise awareness of the causes of ED and its association with more chronic conditions such as cardiovascular disease (CVD) and diabetes. It will encourage treatment seeking behaviour and offer the potential for earlier and more frequent interaction with the primary healthcare system.
- The majority of men with ED are not reporting it to their doctor. The proposal will encourage men suffering from ED and with no known CVD into the healthcare system. This will provide the opportunity for advice and potential diagnosis of underlying CVD, particularly given the 3 to 5 year disease progression from onset of symptoms. There are clear health benefits in being able to bring these men into the healthcare system sooner than currently experienced, given the importance of primary prevention measures such as smoking cessation, regular exercise and healthy diet.
- The efficacy of sildenafil 50 mg has been evaluated in the home setting in a representative group of subjects with ED of broad spectrum aetiology. As well as direct benefits to the consumer, the sildenafil clinical programme demonstrated that partner satisfaction with sexual intercourse also improved. In addition to improving the subject's ED, effective non-prescription treatment with sildenafil can provide broader benefits to improve the subject's quality of life (QoL) and their relationship with their partner.
- The safety profile of sildenafil is well-established based on an extensive controlled clinical trial database and many years of marketing experience with the prescription product. Adverse events (AEs) are generally well-tolerated with very low rates of discontinuation of therapy. The commonly reported AEs in the cumulative clinical trials dataset are consistent with the adverse drug reactions (ADRs) reported in the product information (PI) document, showing that the PI is accurate and comprehensive.
- A detailed assessment of the potential risks associated with non-prescription availability and advertising of sildenafil 50 mg demonstrates that they can be adequately addressed and managed in a non-prescription setting. The [REDACTED] Study has demonstrated that pharmacists can correctly make an assessment with appropriate pharmacy support, based on the proposed non-prescription model. Therefore, usage based on the supply framework for Schedule 3 sildenafil is considered safe and appropriate. A non-prescription status will likely not delay underlying diagnosis but rather encourage treatment-seeking behaviour by allowing the pharmacist to refer men found not suitable for sildenafil 50 mg to a physician for investigation, for potentially earlier diagnosis of any underlying conditions (such as CVD and diabetes). Furthermore, a non-prescription status will not increase misuse/abuse, but instead provide a controlled supply route for those men who are not able or willing to visit their physician in the first instance. This will provide men with the opportunity for

interaction with a healthcare professional (pharmacist) who can provide helpful advice on managing ED and related conditions.

- The non-prescription PI, patient information, and consumer and pharmacist educational programmes have been specifically designed to address the key risks associated with sildenafil 50 mg in a pharmacy setting. These materials include appropriate instructions, contraindications and/or warnings and precautions for use to minimise the key risks identified, i.e. nitrate interactions, priapism and non-arteritic anterior ischemic optic neuropathy (NAION). The materials also allow for clear identification of subjects who are fit for sex and those not fit for sex, to mitigate the hypothetical concern that sildenafil use would indirectly contribute to an increase in the risk of a CV event as a result of enabling sexual intercourse and sexual activity.
- Any incremental risks associated with non-prescription availability and advertising of sildenafil 50 mg can be effectively managed in the pharmacy setting through the following key measures:
 - Pharmacist intervention at the point of sale;
 - Well-developed pharmacist educational programmes;
 - Pharmacist Training Guide and Checklist;
 - PI for healthcare professionals;
 - Product label (primary pack and CMI/leaflet); and
 - Consumer education activities.
- Based on the evidence outlined in the application, the non-prescription sildenafil 50 mg dose has a favourable benefit-risk profile in the pharmacy setting which meets the:
 - Requirements under Section 52E of the *Therapeutic Goods Act 1989*;
 - Scheduling factors for a Schedule 3 Pharmacist Only Medicine in the Scheduling Policy Framework; and
 - Matters set out in the National Coordinating Committee on Therapeutic Goods (NCCTG) guideline for advertising of substances included in Schedule 3.
- The applicant summarises that the important risks for non-prescription sildenafil 50 mg are consistent with those that have been established for sildenafil in the prescription setting. These risks can be effectively managed in the pharmacy setting through routine risk minimisation measures that have been specifically tailored for non-prescription use. Benefits outweigh the risks, and all risks can be appropriately managed through Schedule 3 availability.

Current scheduling status

Sildenafil is in Schedule 4 of the Poisons Standard as follows:

Schedule 4

SILDENAFIL.

The chemically and pharmacologically similar vardenafil and tadalafil are also in Schedule 4 of the Poisons Standard.

Scheduling history

Sildenafil

In August 1998, the National Drugs and Poisons Schedule Committee (NDPSC) noted that sildenafil was widely publicised in the media following its release in the United States of America. The committee members agreed that a Schedule 4 classification should apply from the time sildenafil was marketed in Australia. The committee considered that the contraindications, precautions and drug interactions were such that medical advice was required.

In July 2017, the ACMS considered an application to down-schedule sildenafil to a Schedule 3 Pharmacist Only Medicine. Based on the potential for incorrect assessment of ED by pharmacists, CVD risk, AEs, drug interactions, possible misuse/abuse, risk of worsened outcomes and no upper age limit, the committee recommended, and the delegate agreed, that the current scheduling of sildenafil remains appropriate.

Vardenafil

In June 2003, the NDPSC considered a proposal to schedule vardenafil as a new medicine. The committee decided to list vardenafil in Schedule 4 on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

In November 2016, the ACMS considered a proposal to down-schedule vardenafil in oral preparations containing up to 10 mg to Schedule 3. The committee advised that the current scheduling of vardenafil remains appropriate on the basis that erectile dysfunction can be a marker of an underlying cardiovascular disease, diabetes or endocrine disorder and men should be assessed by a medical practitioner prior to (or at the very least concurrent with) initiation of phosphodiesterase type 5 (PDE5) inhibitor treatment. Furthermore, although vardenafil shows good toxicological profile and is well-tolerated, the cause/aetiology of the medical condition is of greater concern and should first be assessed by a medical practitioner. The committee also noted that PDE5 inhibitors are commonly misused, often in combination with other drugs such as MDMA (ecstasy/methamphetamines). The delegate agreed with the committee's advice, stating that as there are currently no risk management plans for Schedule 3 medicines, it is premature to down schedule vardenafil when there are no mandated requirements to minimise the risk relating to underlying medical conditions. The delegate also noted that no other PDE5 inhibitors have been down-scheduled.

In July 2017, the ACMS again considered an application to down-schedule vardenafil to a Schedule 3 medicine. The committee recommended that the current scheduling of vardenafil remains appropriate based on the potential for incorrect assessment for ED by pharmacists, CVD risk, AEs, drug interactions, possible misuse/abuse, and lack of risk management plans for Schedule 3 medicines. The delegate agreed with the committee's advice and the scheduling of vardenafil remained unchanged.

Australian regulatory history

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has 101 products that contain sildenafil citrate.

In the last 30 years there have been 1104 reported cases of adverse events related to sildenafil in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 974 cases with a single suspected medicine and 42 cases where death was the reported outcome.

According to the [TGA Ingredient Database](#), sildenafil citrate is:

- Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

International regulations

Canada

Health Canada regulates sildenafil as a Prescription Only Medicine. Tablet strengths available include 25 mg, 50 mg and 100 mg, and there is also a 0.8 mg/mL solution of sildenafil registered (as a 10 mg/12.5 mL product) for intravenous use.

New Zealand (NZ)

Medsafe NZ regulate sildenafil as a prescription medicine with the exception of sildenafil for oral use containing 100 mg or less per dose unit sold in the manufacturer's original pack containing not more than 12 dosage units. This is indicated for the treatment of ED in males aged between 35 and 70 years and is provided by a registered pharmacist who has successfully completed a training programme endorsed by the Pharmaceutical Society of NZ.

United States of America (USA)

The USA Food and Drug Administration regulate sildenafil as a Prescription Only Medicine.

United Kingdom (UK)

In November 2017, the [UK Medicines and Healthcare products Regulatory Agency \(MHRA\)](#) formally classified sildenafil 50 mg from a prescription only medicine (POM) to a pharmacy medicine (P). Sildenafil 50 mg could be available without prescription for use by men over 18 who have ED. This decision was made following an assessment of the safety of [REDACTED] advice from the Commission on Human Medicines and a public consultation with positive outcome. Sildenafil 50 mg will be sold in pharmacies following a discussion with the pharmacist. Pharmacists will be able to determine whether treatment is appropriate for the patient and can give advice on ED, usage of the medicine, potential side effects and if further consultation with a general practitioner is required.

[REDACTED] will not be sold to those with severe CVD; at high cardiovascular risk; liver failure; severe kidney failure; or taking certain interacting medicines. Use of [REDACTED] in these groups of men must continue to be under the supervision of a doctor.

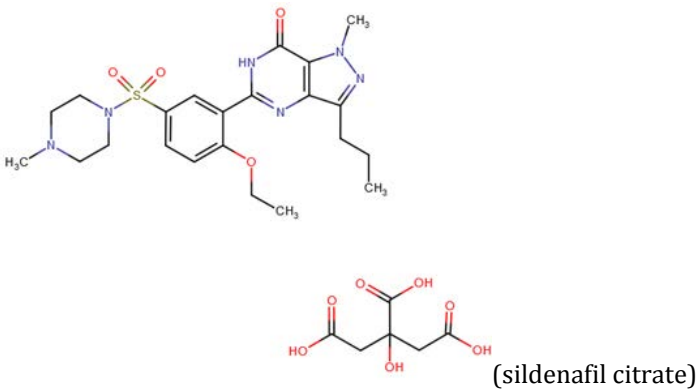
European Union (EU)

An application to switch sildenafil from prescription to OTC in the EU in 2008 was withdrawn by the sponsor after the European Medicines Agency (EMA) noted some concerns. The EMA committee expressed concerns that there would be no medical supervision, which could delay diagnosis of possible CVD. The EMA's Committee for Medicinal Products for Human Use (CHMP) was also concerned that availability of sildenafil through pharmacies could lead to an increase in its recreational use, particularly among younger people.

Substance summary

Sildenafil facilitates penile erection by enhancing the relaxant effect of nitric oxide (NO) released in response to sexual stimulation. Sildenafil citrate, a sildenafil salt, is an orally active selective inhibitor of cyclic guanosine monophosphate (cGMP) specific PDE5. Cyclic-GMP PDE5 is the predominant isoenzyme in the human corpora cavernosa responsible for the degradation of cGMP. By inhibiting PDE5, sildenafil causes NO-induced cGMP concentrations to remain elevated in the corpus cavernosum smooth muscle. Elevated cGMP levels signal smooth muscle relaxation, resulting in an inflow of more blood in the corpus cavernosum and subsequent penile erection.^{9, 10} To be effective, sexual stimulation is required.

Table 1.1: Chemical properties of sildenafil

Property	Sildenafil (as citrate)
CAS number	171599-83-0 (as citrate)
IUPAC and/or common and/or other names	5-[2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-D]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3- tricarboxylic acid.
Chemical structure	 (sildenafil citrate)
Molecular formula	C ₂₂ H ₃₀ N ₆ O ₄ S.C ₆ H ₈ O ₇ (as citrate)
Molecular weight	666.7 g/mol (as citrate)

⁹ Boolell M, Allen MJ, Ballard SA, *et al.*, Sildenafil: An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996;8(2):47-52.

¹⁰ Burnett AL. Role of nitric oxide in the physiology of erection. *Biol Reprod* 1995;52(3):485-9.

Pre-meeting public submissions

Eleven (11) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. Seven (7) submissions supported the proposed amendment (one did not support the proposed Appendix H entry), and four (4) opposed the proposed amendment.

The main points provided in support of the amendment were:

- General statements on the proposal:
 - The prevalence of ED reported in Australia and NZ has ranged between 25-40% of men.¹¹ However, only 14-16% of men sought a medical diagnosis and treatment to manage their condition despite the increase in public awareness and acknowledgement of ED since the development of effective pharmacological treatments such as sildenafil.
 - Australian men are less likely than women to seek treatment from a GP or other health professional. Pharmacists have been repeatedly voted as one of the top three regarded professions in Australia. It is believed that men will be more willing to discuss their health with their pharmacist. Further, appointments with pharmacists are not required.
 - Risk factors such as smoking, hypertension, obesity and high total cholesterol levels all contribute to ED. If risk factors are identified during the consultation/screening, the pharmacist can refer them to a doctor. As a result, more men would enter into the healthcare system. This opportunity can potentially slow or halt the progression of diseases such as CVD.
 - Men with low CVD risk can be readily identified by a pharmacist, can begin ED treatment without further testing and can initiate/resume sexual activity quicker. This will reduce the burden on GPs.
 - The proposal meets the scheduling factors for a Schedule 3 medicine.
 - A lack of an upper age limit in the proposed Schedule 3 entry is not a valid reason for rejection. Men that fall into this category will be identified by the pharmacist and referred to their GP.
 - A similar scheduling arrangement has existed in NZ since 2014 and results have been positive. The UK regulator recently re-classified sildenafil to a Pharmacy Medicine.
 - Allowing sildenafil to be available without a prescription will provide greater opportunities for men to be screened for CVD, be provided health advice and be referred to a doctor if necessary.
- Proposed Appendix H entry:
 - An Appendix H entry will lead to more men having earlier discussions with a health professional, help raise public awareness of the Schedule 3 availability of sildenafil and deliver a range of benefits to both consumers and pharmacists.

¹¹ Chew, KK, Stuckey B, Bremner A, Earle C, Jamrozik K. [Male Erectile Dysfunction: Its Prevalence in Western Australia and Associated Sociodemographic Factors](#). Journal of Sexual Medicine. 2008; 5(1): 60–69 and Quilter M, Hodges L, Von Hurst P, Borman B, Coad J. [Male Sexual Function in New Zealand: A Population-Based Cross-Sectional Survey of the Prevalence of Erectile Dysfunction in Men Aged 40–70 Years](#). Journal of Sexual Medicine. 2017;14(7): 928–36.

- Proposed Appendix M entry:
 - The concern from a previous ACMS meeting that ‘additional pharmacist training and use of a specific supply protocol cannot be mandated for the supply of pharmacist-only Schedule 3 medicines’ has now been addressed through the establishment of Appendix M. Other concerns that were raised by the delegate will also be mitigated by the proposed Appendix M entry and associated mandatory pharmacist training/protocols. This will ensure that Quality Use of Medicines (QUM) principles are met.
 - Community pharmacists have the capacity be trained in the diagnosis and management of ED. This will enable pharmacists to encourage men to seek further medical care if required, increasing the chance of early detection of undiagnosed comorbidities such as CVD, metabolic syndrome and diabetes. This training will also enable pharmacists to educate men, helping them to overcome the stigma of ED and in turn increasing the likelihood that they will seek health advice from their GP.
 - The Schedule 3 protocols will be a systematic, evidence-based procedure that will assist pharmacists to fulfil their professional obligations. Key elements of guidelines will consider similar guidance in NZ and the UK, but would be contextualised for Australian practice. This would provide a robust, evidence-based clinical assessment process to identify men found suitable for supply and expectations for medical referral when not appropriate.
 - Men already diagnosed with type 2 diabetes would be under the care of their GP and would be regularly consulted on the management of their condition. This regular consultation would provide them with the opportunity to discuss any concerns regarding ED. Men with undiagnosed type 2 diabetes will benefit from a pharmacist screening using the protocol as they will be referred to a GP.
 - The risk of men not disclosing contraindications to a pharmacist is mitigated by pharmacists being trained to explain the importance of disclosure. This risk is likely to be the same for pharmacists as it is for doctors.
 - Repeat supplies for sildenafil will require assessment using the protocol to ensure that the patient’s condition had not changed. This will provide an opportunity for those men at higher risk to have a full medical investigation.
- Safety of sildenafil:
 - Sildenafil has a well-established safety profile and is well tolerated. Adverse events of sildenafil are generally transient and mild to moderate in nature. Data from systematic reviews, case reports and pharmacovigilance monitoring systems support the safety and tolerability of PDE5 inhibitors. The TGA’s DAEN reports for sildenafil products indicate relatively minor adverse events that mostly align with the PI. Considering the history of sildenafil prescribing in Australia (available for over 20 years), the number of reports is relatively minor.
 - Sildenafil has been extensively studied. Numerous studies have demonstrated the safety of PDE5 inhibitors, including a reduction in all-cause mortality, dose dependent reduced risk of death or heart failure and independent protection against mortality in men with diabetes. The risk of a serious adverse event occurring is extremely low.
 - Sildenafil is not addictive and has a very low abuse potential. MedWatch reported 44 separate warnings of abuse since 2000, most of which reported contamination of herbal products with active drug components.

- Performance of a CV assessment and collection of medical history is not required prior to commencing treatment with a PDE-5 inhibitor for all men with ED. The Princeton III Consensus states that men deemed to be 'low risk' can initiate or resume sexual activity and begin ED treatment without further testing or evaluation.¹²
- Drug interactions:
 - Potential drug-drug interactions involving sildenafil are unlikely to be an issue as they will be identified by the pharmacist. The only serious drug-drug interaction is with nitrates and riociguat. Those interactions will be highlighted on the pack. In most cases, sildenafil – nitrate interactions involve transient hypotension and are not associated with serious adverse events leading to incapacitation or hospitalisation.
 - Any patient taking nitrates would have been prescribed these by their GP and would be aware of their clinical diagnosis. It is assumed they would be regularly visiting their GP for this and they would have the opportunity to discuss their suspected ED. In the event that they requested a supply of sildenafil from a pharmacist, these medicines would be identified as part of the protocol and the pharmacist would refer them back to their doctor.
 - Contraindications will be addressed by appropriate labelling.
- Counterfeit sildenafil:
 - ED medicines are currently the most counterfeited medicines seized by UK customs, suggesting that the market for these drugs is large. ED medicines from uncontrolled sources are often of poor quality, have an unknown amount of active, contain the wrong ingredient and often have no appropriate patient information.
 - There are a growing number of TGA alerts relating to contaminated, adulterated and counterfeit ED products. Men who purchase these products are doing so without the supervision of a healthcare professional. Increased access of sildenafil without a prescription will provide men with a legitimate product and advice from a pharmacist.
 - Access to sildenafil from a pharmacist following a consultation would likely reduce counterfeit purchasing from internet websites. Men consulting their pharmacist are more likely to engage with their doctor if the pharmacist has identified any risk factor.

The main points provided in opposition of the amendment were:

- The potential benefits of re-scheduling sildenafil to Schedule 3 do not outweigh the potential risks to patient safety. Re-scheduling sildenafil will not help destigmatise ED or lead to improvements in treatment seeking behaviour for chronic medical conditions.
- The same proposed amendment for sildenafil was made in mid-2017 and a similar proposal for vardenafil was made in the mid-2016. Both applications were subsequently rejected by the ACMS.
- ED is complex medical condition, is a marker for the state of the blood vessels and should be thoroughly investigated before PDE5 inhibitors are prescribed. This is best investigated by the patient's usual GP where this issue can be teased out and, if appropriate, alternatives discussed. ED may also be caused by many other prescription medicines. It is also crucially important to explore whether there are psychological causes of ED which can be a very

¹² Nehra A, Jackson G, Miner M, *et al.*, The Princeton III Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease. *Mayo Clin. Proc.* 2012; 87: 766-78.

significant reason for presentation. These issues cannot be addressed by answering a simple checklist of questions posed by a pharmacist.

- Pharmacists in the community setting do not have the adequate resources to screen for these risks, irrespective of any Appendix M entry that would mandate the pharmacist to undertake accredited Continuing Professional Development and use a patient assessment tool. The contents of any patient assessment and screening tool must be consulted on and validated by expert clinicians.
- It is argued that men will be more likely to seek help for ED from a pharmacist rather than make an appointment with their GP. Men who have not attempted to obtain prescription sildenafil from a GP will not be more comfortable obtaining non-prescription sildenafil from a pharmacist. Further, accessing these medicines from a pharmacist does not avoid initiating a conversation about ED. Conversations with men regarding ED can be very difficult to initiate when there is no well-developed therapeutic relationship between doctor and patient. It is most unlikely that a pharmacist delivered checklist will facilitate the confidence, trust and emotional security to entertain such a delicate discussion.
- Once ED issues are broached, a consultation with a GP will ensure that a full health assessment is undertaken, risk factors are identified and holistic advice is provided. A GP consultation to obtain a sildenafil prescription also provides an opportunity to screen for diabetes mellitus and sexually transmissible infections, as well as undertake unrelated but important health prevention activities.
- There are potential and serious adverse reactions associated with use of sildenafil including (but not limited to) prolonged QT intervals and an increased risk of arrhythmias. There are also a significant range of contraindications. Identification and management of these contraindications is most appropriately assessed by a GP for the first prescription.
- Sildenafil has serious interactions with a range of other medicines. While a pharmacist may theoretically know about a patient's usual medicines, a patient's regular GP will also know the full range of medicines currently prescribed, why those particular medicines were prescribed, and be able to discuss safe alternative approaches. A pharmacist identifying a potential adverse drug interaction will, in any event, have to refer the patient to their GP.
- A pharmacist-administered questionnaire, even if supported by additional training provided by the sponsor, will not mitigate the risks to patient safety or ensure dispensing and use that is consistent with QUM principles.
- It should be noted that pharmacists will gain financially from the dispensing of these medicines which is an inherent conflict of interest.
- Data from a poisons line indicates the potential harms and misuse of PDE5 inhibitors such as sildenafil which would be expected to increase with more widespread availability without a prescription. PDE5 inhibitor exposure has a high rate of hospital referral (91%) compared to other pharmaceuticals.

ACMS advice

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

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

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

The reasons for the advice included:

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

- Sildenafil does not meet the Schedule 3 SPF criteria because:
 - § Risk of ED treatment without medical diagnosis or treatment of any underlying serious medical conditions (such as cardiovascular disease and diabetes) outweighs benefit of making sildenafil available as a Schedule 3 medicine.
 - § The list of diagnosis tools (including ECG and other cardiac testing) recommended by the Princeton III report is not possible in a pharmacy setting.
- ED is an independent risk factor of cardiovascular disease.
- There is no evidence that the patient will consult with their GP at the advice of their pharmacist.
- There is no evidence that the benefits of improved access for consumers are greatly outweighed by the risk of improper diagnosis or treatment of erectile dysfunction or associated risk factors by a pharmacist.

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

- Although both patients and pharmacists can identify erectile dysfunction, the risk of facilitating ED treatment without appropriate diagnosis or treatment of any underlying serious medical conditions is too great to recommend sildenafil be moved to Schedule 3.
- Erectile dysfunction – on an ‘as necessary’ basis

(c) the toxicity of a substance:

- Although sildenafil has well known side-effects and drug interactions, the risk of facilitating ED treatment without appropriate diagnosis or treatment of any underlying serious medical conditions is too great to recommend sildenafil be moved to Schedule 3.
- Main risk is hypotension. Sildenafil has a significant adverse effect profile that requires medical monitoring. Drug-drug interactions may potentiate sildenafil toxicity.

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

- Limited pack size is considered to not appropriately address risk of harms to consumers brought about by a lack of medical oversight in supply of sildenafil.

(e) the potential for abuse of a substance:

- Misuse by men without erectile dysfunction is already known to occur, including in combination with illicit drugs such as MDMA.
- Issues with counterfeit sildenafil are recognised, however increasing consumer access to sildenafil through down scheduling is not considered an appropriate mechanism to address this problem.

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

- Educational campaigns to raise awareness of the association between erectile dysfunction and serious medical conditions and to direct men to discuss their sexual function with their GP can be undertaken, without requiring sildenafil to be down-scheduled.
- Overcoming stigma with erectile dysfunction and improving treatment rates would be better addressed through consumer education and information.
- No new relevant evidence supporting the down scheduling to schedule 3 was provided in the submission.
- No appendix M training and checklist information was provided for the Australian context in managing ED.
- Questionability of whether appendix M is appropriate for ED and sildenafil treatment given that ED is a symptom of other conditions requiring medical practitioner monitoring and treatment.
- A public health campaign would be beneficial in raising awareness of ED independently of potential medical treatments or down-scheduling sildenafil.
- It was suggested by the committee that guidance be developed in relation to the content of Appendix M.

§ There was no proposed appendix M education and checklist material included in the submission so until this was provided, it is difficult to assess whether an Appendix M listing would mitigate the risks of down scheduling. An appendix M listing would need to address:

- * Development of accredited competency-based training for pharmacists by an appropriate accredited training body.
- * Pharmacists are required to have written documentation of their consultation, outlining the clinical assessment they undertook and whether they supplied medication or referred.
- * Well-developed clinical referral pathways for pharmacists that must be adhered to.

1.2 Budesonide

Delegate's 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 budesonide as follows:

Schedule 2 – Amend Entry

BUDESONIDE in aqueous nasal sprays delivering ~~506~~⁴ micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms ~~and when packed in a primary pack containing 200 actuations or less~~, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Proposed implementation date: **1 February 2019**

Reasons:

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

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

- Intra-nasal corticosteroids (INC) are a first-line recommended treatment for allergic rhinitis and are associated with minimal risks.
- The proposed change does not alter the recommended dose maximum daily dose.
- Intranasal corticosteroids such as budesonide are well-established as recommended agents for effective long-term management of symptoms of allergic rhinitis. There is almost 30 years' experience with budesonide in Australia including 20 years non-prescription experience.
- Long-term safety profile has been established from clinical trials and extensive post-marketing data with insignificant systemic absorption of budesonide used nasally or from any portion of the dose that is swallowed.
- Making budesonide available in a larger pack size is unlikely to impact the risk-benefit profile significantly.
- Making budesonide available in a higher strength dose means less frequent administration by the consumer to achieve the maximum recommended dose. This is unlikely to impact the risk-benefit profile significantly.

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

- The purpose for which budesonide is used is for the symptomatic treatment and prophylaxis of allergic rhinitis in adults and children over 12 years. Intra-nasal corticosteroids such as budesonide are a first-line recommended treatment for allergic rhinitis.

(c) the toxicity of a substance:

- Budesonide has high tolerability and safety with low frequencies of adverse events in clinical trials and post-marketing. There have been no significant adverse events

attributable to budesonide nasal sprays since their inclusion in Schedule 2.

- Local adverse effects related to oropharyngeal and septal exposures are minor and minimised through appropriate inhalation technique.

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

- Availability of a second, higher strength product would allow reduced number of doses to achieve same maximum daily dose. Product labelling can be used to differentiate the two products;
- A reduction in the number of sprays required to achieve the desired dose increases convenience for the consumer and may assist with compliance.
- Removing the actuation limit will allow new larger pack sizes and provide a longer duration of treatment;
- Access to a higher strength product will result in enhanced compliance, symptom control, quality of life, and reduced medicine and healthcare resource costs.

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

- This change to the scheduling of budesonide in the Poisons Standard will align the Schedule 2 entry with other intranasal corticosteroids.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to budesonide;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- 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; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for budesonide

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to budesonide. The application proposed to amend the Schedule 2 entry of budesonide.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 2 – Amend Entry

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

The applicant's reasons for the proposal were:

- Budesonide is a potent synthetic glucocorticosteroid with special kinetic properties. In non-clinical pharmacological studies, budesonide demonstrates a wide variety of anti-allergic and anti-inflammatory effects.
- Current range of Schedule 2 inhaled nasal corticosteroids (INCs) are only available in one strength, which in effect means that delivered dosage and treatment effectiveness are very much dependent on consumers' willingness and compliance to administer the full number of required sprays per day.
- INCs (including budesonide) are recommended first-line allergic rhinitis (AR) treatment choices in both Australian and international clinical guidelines.
- While AR is not life-threatening, it is of substantial public health significance. AR is widely considered as the most common chronic respiratory disorder. Reported prevalence varies considerably as it is often underdiagnosed. It affects between 23% and 50% of the population worldwide with progressively increasing prevalence in more-developed countries. In Australia, the current prevalence is in excess of 15% (or 3.7 million of the current population) with a predicted estimate of 27% in 2050.
- For the individual AR sufferer, symptoms can have a significant impact on the quality of life, often resulting in sleep disturbance, fatigue and an impaired ability to concentrate, learn, and make decisions. In addition to the physical discomfort, AR symptoms have been associated with a reduction in worker productivity, student performance, and higher absenteeism rates from work and school, resulting in 3.5 million lost workdays and 2 million lost schooldays annually in the United States of America (USA). Fifty six per cent of Australian AR sufferers report that their symptoms have a moderate-to-severe impact on their quality of life and 61% report interference with work/school.
- AR is a condition that has been well established as suitable for both self-diagnosis and self-treatment. Symptoms of AR, including sneezing, runny nose, itchy nose and nasal congestion, are easily identifiable by both allergy sufferers and parents.
- People who need to continue with the maximum dose of budesonide to maintain symptom control will benefit from the convenience of the proposed Schedule 2 64 µg strength, which requires only 4 sprays per day compared to the current 8 sprays per day.

- The proposed amendment to the Schedule 2 entry for budesonide is one strategy that is likely to improve AR compliance and treatment outcomes and have a potentially broad positive healthcare impact. No changes have been requested to the current Schedule 2 budesonide entry in regards to the 400 µg daily dosage or the 6-month dosage period limits.
- In 2006, the National Drugs and Poisons Schedule Committee (NDPSC) agreed that budesonide should have a fully harmonised INC Schedule 2 entry including 5 restriction criteria – formulation, strength, dosage, indication and age. They also agreed to remove the pack size restriction criteria. However, it appears that during implementation of the harmonised Schedule 2 budesonide scheduling entry in February 2007, the pack size restriction criteria was reinstated without a clear rationale.

Current scheduling status

Budesonide is listed in Schedules 2 and 4 of the Poisons Standard as follows:

Schedule 2

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

Schedule 4

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

Scheduling history

The scheduling history for budesonide for intra-nasal use is outlined below.

In November 1990, the Drugs and Poisons Schedule Committee (DPSC) included budesonide in Schedule 4 after receiving an application for use in bronchial asthma and AR.

In November 1998, the NDPSC agreed to include budesonide in Schedule 3 in aqueous nasal sprays delivering 50 micrograms per actuation when the maximum recommended daily dose is no greater than 400 micrograms, for the treatment of seasonal and AR. The Schedule 4 entry was also amended to include 'except when included in Schedule 3'.

In February 1999, the NDPSC agreed to amend the Schedule 3 entry for budesonide to 'budesonide in a dose of 50 microgram or less' to allow the supply of lower dose preparations.

In August 1999, the NDPSC agreed to amend the typographical error in Schedule 3 of 'seasonal and allergic rhinitis' to read 'seasonal allergic rhinitis'. The Schedule 3 entry was also amended to include 'and when packed in a primary pack containing 200 actuations or less' and 'in adults and children 12 years and over'.

In August 2000, the NDPSC agreed to amend the Schedule 3 entry for budesonide to include 'for the short-term prophylaxis'. The committee also agreed to include budesonide in Appendix H based on its similarity of other nasal corticosteroids which are permitted to be advertised.

In October 2002, the NDPSC agreed to amend the Schedule 3 entry for budesonide to include perennial allergic rhinitis (PAR) based on post-marketing safety data and no expected safety issues to arise from the short-term use of intranasal budesonide for the prophylaxis or treatment of allergic rhinitis.

In June 2003, the NDPSC agreed reschedule budesonide in aqueous nasal spray to Schedule 2 for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adult and children 12 years and over based on extensive local and overseas experience, AR not requiring medical diagnosis and is easily diagnosed by the consumer and supporting information that budesonide is substantially safe in adults and children 12 years and over.

In October 2005, the NDPSC agreed to consider removing the pack size restriction 'when packed in a primary pack containing 200 actuations or less' from the Schedule 2 entry at the February 2006 meeting to harmonise with New Zealand (NZ).

In February 2006, the NDPSC agreed to amend the Schedule 2 entry for budesonide by removing the limit of actuations, thereby harmonising with NZ.

In February 2007, the NDPSC amended the Schedule 2 entry for budesonide for clarity and consistency by adding 'of age' after '12 years'.

Australian regulations

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has 43 products that contain budesonide. The products marketed include nasal sprays, metered dose inhalers, inhalation ampoules, dry power inhalers, enteric capsules and nebuliser suspension.

Budesonide does not appear in the current [Therapeutic Goods \(Permissible Indications\) Determination No. 2 of 2018](#) as it is a scheduled substance and is not eligible for use in ARTG listed medicines.

In the last 30 years there have been 521 reported cases of adverse events related to budesonide in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 319 cases with a single suspected medicine and 7 cases where death was the reported outcome.

According to the [TGA Ingredient Database](#), budesonide is:

- Available for use as an Active Ingredient in Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Available for use as an Excipient Ingredient in Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

International regulations

Canada

In Canada, 64 µg budesonide nasal sprays are regulated as a prescription medicine.

United Kingdom (UK)

In the UK, 64 µg budesonide nasal sprays are regulated as an over-the-counter (OTC) medicine.

NZ

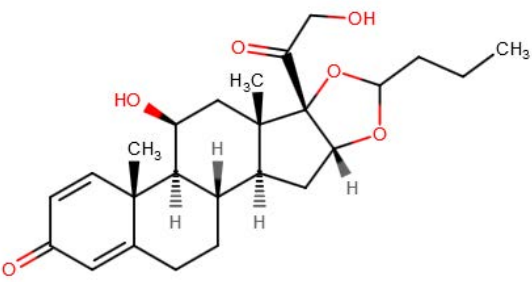
Medsafe NZ regulate budesonide as a Pharmacy Only medicine for the treatment or prophylaxis of allergic rhinitis in adults and children over 12 years of age in aqueous nasal sprays delivering up to 50 micrograms per actuation and when the maximum recommended daily dose is no greater than 400 micrograms (200 micrograms per nostril) in a pack containing 200 actuations or less.

USA

In the USA, 32 µg budesonide nasal sprays are regulated as an over-the-counter (OTC) medicine.

Substance summary

Table 1.2: Chemical information for budesonide

Property	Budesonide
CAS name	51333-22-3
IUPAC and/or common and/or other names	(11-beta,16-alpha)-16,17-(Butylidenebis(oxy))-11,21-dihydroxypregna-1,4-diene-3,20-dione
Chemical structure	
Molecular formula	C ₂₅ H ₃₄ O ₆
Molecular weight	430.5 g/mol

Budesonide is a potent synthetic glucocorticosteroid with special kinetic properties. It has a high affinity for the glucocorticosteroid (aka ‘corticosteroid’ or simply ‘steroid’) receptor, and in non-clinical pharmacological studies demonstrates a wide variety of anti-allergic and anti-inflammatory effects.¹³ Budesonide inhibits the production and release of a variety of mediators and cytokines from inflammatory cells. Moreover, budesonide inhibits the immediate and late phase allergic reactions, bronchial hyperreactivity and cellular infiltration after provocation.

INCs currently marketed in Australia to treat AR are broadly characterised according to their absorption characteristics, with first-generation including beclomethasone, triamcinolone and budesonide considered hydrophilic molecules, and second-generation molecules mometasone, ciclesonide and fluticasone considered lipophilic.^{14,15} While higher lipophilicity is one pharmacological characteristic that may lead to varied local and systemic absorption, safety and efficacy of INCs is influenced by mucosal solubility (higher hydrophilicity reduces mucociliary clearance) and nasal metabolic pathways inhaled device delivery efficiency.^{16,17} Budesonide’s

¹³ Edsbacker, S., 1999. Pharmacological factors that influence the choice of inhaled corticosteroids. *Drugs*, 58(Suppl 4), pp. 7-16.

¹⁴ Sastre, J., Mosges, R., 2012. Local and Systemic Safety of Intranasal corticosteroids, *Journal of Investigations into Allergology and Clinical Immunology*, 22(1), pp.1-12.

¹⁵ Chong, L., Head, K., Hopkins, C., Philpott, C., Burton, M., Schilder, A. 2016. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database of Systematic Reviews* 4. [DOI: 10.1002/14651858.CD011993.pub2].

¹⁶ Miller-Larsson, A., Jansson, P., Runström, A., Brattsand, R., 2000. Prolonged airway activity and improved selectivity of budesonide possibly due to esterification. *American Journal of Respiratory and Critical Care Medicine*, 162, pp.1455-61.

¹⁷ Lipworth, B., Jackson, C., 2000. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Safety*, 23(1), pp.11-33.

unique reversible fatty acids esterification pathway is believed to contribute to its long duration of action within the airways/lung.¹⁸

High hepatic metabolism of any swallowed INC dose also contributes to minimise systemic exposure. Budesonide undergoes extensive biotransformation (approximately 90%) on first-passage through the liver to metabolites of 100-fold lower activity than the parent compound.^{19,20}

Pre-meeting public submissions

Four (4) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. All four (4) submissions were in support of the proposed amendments.

The main points provided in support of the amendment were:

- Budesonide has been available in Australia since 1990 and as an aqueous nasal spray since 2001 for the prophylaxis and treatment of both seasonal and perennial AR. The scheduling proposal will align schedule entries for budesonide with other INCs.
- INCs are recommended for first-line therapy if symptoms are persistent and/or moderate to severe, and are more effective than oral antihistamines for AR.
- Treatment of AR may need to be continued for lengthy periods of time, and in some cases for many years. The inclusion of a maximum number of actuations may be unnecessary and be related to the expiry date of the particular formulation after opening.
- The primary goals of treatment of allergic rhinitis are to reduce symptoms, and to improve quality of life and daily functioning. INC sprays have high efficacy in controlling symptoms of AR and a good safety profile, with minimal risk of systemic side effects due to their low bioavailability. Further, INC sprays containing budesonide are well tolerated. There have not been any significant adverse events attributable to budesonide nasal sprays since their inclusion in Schedule 2.
- Two strengths of the nasal spray are currently available; 32 µg per actuation (Schedule 2) and 64 µg per actuation (Schedule 4). When used as recommended, the two product strengths provide the same total daily dose of budesonide. However, the 64 µg product offers a more comfortable and convenient application. It is to be expected that the less frequent application will lead to better adherence and clinical outcomes. Product labelling can be used to effectively differentiate between the two products.
- The proposal has the potential to improve adherence. Two hundred (200) actuations corresponds to about 3.5 weeks' usage of the 32 µg product and about 7 weeks' usage of the 64 µg product. Effective long-term management of AR typically involves longer periods of continuous use.
- Both the 32 µg per actuation product and the 64 µg per actuation product meet the scheduling factors for Schedule 2.

¹⁸ Tunek, A., Sjodin, K., Hallstrom, G., 1997. Reversible formation of fatty acid esters of budesonide, an antiasthma glucocorticoid, in human lung and liver microsomes. *Drugs and Metabolic Disposition*, 25, pp. 1311-7.

¹⁹ Johnson & Johnson Pacific Pty Ltd. *Rhinocort (budesonide) Product Information*, Most recent amendment [at time of this submission]: 2017 August

²⁰ Jonssön G, Åström A, Andersson P. Budesonide is metabolized by cytochrome P450 3A(CYP3A) enzymes in human liver. *Drug Metabolism and Disposition* 1995;23:137-42.

- Budesonide has been the subject of numerous clinical studies and its safety and efficacy are well characterised. If there is no clinical justification for the inclusion of 'containing 200 actuations or less' in the budesonide entry then it should be removed. The proposal to remove the actuation limit is also consistent with the Schedule 2 entry for mometasone and with the recent proposal to remove the actuation limit from the Schedule 2 entry for fluticasone.

ACMS advice

The committee recommended that the Schedule 2 entry be amended as follows:

Schedule 2 – Amend Entry

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

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

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

The reasons for the advice included:

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

- Intra-nasal corticosteroids are a first-line recommended treatment for allergic rhinitis and are associated with minimal risks.
- The proposed change does not alter the recommended dose maximum daily dose.
- Almost 30 years' experience with this agent in Australia including 20 years non-prescription experience. Intranasal corticosteroids such as budesonide are well-established as recommended agents for effective long-term management of symptoms of allergic rhinitis. Long-term safety profile established from clinical trials and extensive post-marketing data with insignificant systemic absorption of budesonide nasally or any portion of dose that is swallowed.
- Making the agent available in a larger pack size is unlikely to impact the risk:benefit profile significantly.
- Making the agent available in a higher strength dose means less doses that the consumer needs to administer (ie one dose vs two doses) to achieve the maximum recommended dose. This is unlikely to impact the risk:benefit profile significantly.

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

- Intra-nasal corticosteroids are a first-line recommended treatment for allergic rhinitis.
- Symptomatic treatment and prophylaxis of allergic rhinitis in adults and children over 12 years.

(c) the toxicity of a substance:

- There have not been any significant adverse events attributable to budesonide nasal sprays since their inclusion in Schedule 2.
- Local adverse effects related oropharyngeal and septal exposure are minor and minimised through appropriate inhalation technique.
- High tolerability and safety with low frequencies of adverse events in clinical trials and post-marketing.

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

- Reduction in the number of sprays required to achieve the desired dose increases convenience, may assist with compliance. The reduced treatment burden might result in more consistent inhalation technique and potential result in a reduced risk of oropharyngeal and septal drug exposure.
- Removal of actuation limit would allow new pack size availability providing longer duration of treatment;
- Availability of a second, higher strength product would allow reduced number of doses to achieve same max daily dose. Product labelling can be used to differentiate the two products;
- Both factors enhance adherence, symptom control, quality of life, and reduced medicine and healthcare resource costs.

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

- This change will align the Schedule 2 entry with other intranasal corticosteroids.

1.3 Alkyl nitrites

Delegate's 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 alkyl nitrites and lubricants as follows:

Schedule 4 – Delete Entries

~~AMYL NITRITE.~~

~~BUTYL NITRITE.~~

~~ISOAMYL NITRITE.~~

~~ISOBUTYL NITRITE.~~

~~OCTYL NITRITE.~~

Schedule 9 – New Entries

ALKYL NITRITES **except** those specifically listed elsewhere in these Schedules.

ISOPROPYL NITRITE.

PROPYL NITRITE.

CYCLOHEXANE NITRITE.

Schedule 9 – Entries moved from Schedule 4

AMYL NITRITE.

BUTYL NITRITE.

ISOAMYL NITRITE.

ISOBUTYL NITRITE.

OCTYL NITRITE.

Appendix A – Amend Entry

LUBRICANTS **in preparations that provide a lubricating action between machinery parts, except** soluble oils and solvent-deposited lubricating agents.

Proposed implementation date: 1 February 2019

Reasons:

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

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

- There are numerous risks of harm associated with alkyl nitrites.
- Risks associated with the use of alkyl nitrites include illicit use for euphoric (perceived due to dilation of blood vessels in brain and periphery), analgesic and muscle relaxant effects.²¹
- Adverse events associated with the use of alkyl nitrites include methaemoglobinaemia

²¹ Docherty et al (2017) "Poppers Maculopathy": a case report and literature review', *Canadian Journal of Ophthalmology*, In press.

DOI: <https://doi.org/10.1016/j.ijcio.2017.10.036>

and maculopathy.^{21,22, 23} Complete recovery of visual function even after drug use is ceased is rare.²⁴ According to a 2016 UK government report (Advisory Council on the Misuse of Drugs) there are around 30 published cases of ophthalmological damage associated with use of alkyl nitrites.

- Alkyl nitrites are toxic via inhalation. Toxicity includes tachycardia, hypotension, headache, flushing, dizziness, nausea, and syncope.²⁵ Co-use with phosphodiesterase type 5 (PDE-5) inhibitors can lead to severe hypotension.
- Increased risk of cardiovascular harm when used in conjunction with other vasodilators.
- Alkyl nitrites are sweet-smelling liquids and pose a risk to child safety through cases of accidental ingestion.
- There appears to be an increasing trend with time in the use and abuse of volatile alkyl nitrites, with a 56% increase in exposures from 2009 to 2014 according to statistics collected from Australian Poisons Information Centres.
- Over an eleven year period (2004-2014), Australian Poisons Information Centres received 273 calls about alkyl nitrite exposures:
 - § 3.7% of calls (10 cases) which involved accidental paediatric exposures.
 - § Hospitalisation was required in 72.5% of all cases with almost all of these requiring a clinical toxicology consultant, indicating high perceived risk or severity.
 - § 15% (41 cases) of the hospital admitted patients presented with methaemoglobinaemia, with 14 requiring treatment with the antidote, methylene blue.
- There are no therapeutic benefits associated with the use of alkyl nitrites other than amyl nitrite, which may be used as an alternative antidote for cyanide poisoning in the event that IV access or first line antidotes are not immediately available.
- Industry stakeholders have not identified any current use of alkyl nitrites and have indicated that the proposed changes to the Poisons Standard with respect to alkyl nitrites and lubricants will therefore not impact their current products.

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

- Commonly misused alkyl nitrites include amyl nitrite, butyl nitrite and isobutyl nitrite, with more recent variations including isopropyl and cyclohexyl nitrite.
- Alkyl nitrites have little to no therapeutic use. There are no products on the Australian Register of Therapeutic Goods (ARTG) that contain alkyl nitrites. There are no agricultural products or veterinary medicines containing any nitrite listed on the Australian Pesticides and Veterinary Medicines Authority's PubCRIS database.
- Volatile nitrites were historically used to treat angina²⁶ however they have been replaced by other medications.
- There is limited and superseded therapeutic use for amyl nitrite as an antidote for

²² Tiew S, Choudhary A. (2015) 'Poppers maculopathy or retinopathy?' *Eye*. 29, 147-8

²³ Hunter, L. et al., (2011) 'Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: A review', *British Journal of Clinical Pharmacology*, 72(1), pp.18-26

²⁴ Audo, I. et al., 2011. Foveal damage in habitual poppers users. *Archives of Ophthalmology*, 129(6), pp.703-708.

²⁵ Romanelli, F. et al., (2004) 'Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse', *Pharmacotherapy*, 24(1), pp.69-78

²⁶ Fye WB, (1986) 'T Lauder Brunton and amyl nitrite: a Victorian vasodilator', *Circulation*, 74, 222-9

cyanide poisoning. Current alternative treatment recommendations for cyanide poisoning include sodium thiosulfate plus hydroxocobalamin, or sodium nitrite plus sodium thiosulfate.²⁷

- Alkyl nitrites are largely used recreationally as ‘party drugs’. There has been an increase in the use and abuse of alkyl nitrites in Australia over recent years. According to the most recent 2017 report of the Ecstasy and Related Drugs Reporting System (EDRS)²⁸ recent users of alkyl nitrites was reported in 25% of study participants.

(c) the toxicity of a substance:

- Alkyl nitrites are toxic via inhalation. Toxicity includes tachycardia, hypotension, headache, flushing, dizziness, nausea, and syncope.²⁹ Co-use with phosphodiesterase type 5 (PDE-5) inhibitors can lead to severe hypotension.
- Increased risk of cardiovascular harm when used in conjunction with other vasodilators.
- Inhalation of alkyl nitrites can lead to methaemoglobinaemia and even death, with significantly increased risk if ingested. Methaemoglobinaemia is potentially life threatening if not treated appropriately.²³
- Alkyl nitrites can cause chemical burns to the skin and eyes on direct contact. Other risks of alkyl nitrites include maculopathy and skin lesions.

(e) the potential for abuse of a substance:

- There is a high potential for misuse and abuse of alkyl nitrites for euphoric properties, and as sex aids due to their muscle relaxant properties.
- The misuse and abuse of alkyl nitrites appears to be in particular sections of the community rather than widespread.

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

- Exemptions from scheduling for lubricants were first proposed in 1965 and in 1969 and ‘motor fuels and lubricants’ were included in the list of exemptions at this time. Amendments to the Appendix A lubricant entry will clarify its intent, restricting the Appendix A exemption under the Poisons Standard to machinery use, not personal care use.
- Feedback from those supplying industrial machinery lubricants did not identify any problems with the proposed new wording for the Appendix A entry.

Delegate’s considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to alkyl nitrites;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- The public submissions received before the first closing date;

²⁷ Therapeutic Guidelines, Toxicology and Wilderness, Therapeutic Guidelines Ltd (eTG March 2018 edition)

²⁸ [The Ecstasy and Related Drugs Reporting System \(EDRS\)](#)

²⁹ Romanelli, F. et al., (2004) ‘Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse’, *Pharmacotherapy*, 24(1), pp.69–78

- 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; (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 was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for alkyl nitrites

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to alkyl nitrites. The application proposed to amend the Appendix A listing for lubricants and to create a new Schedule 4 group entry for alkyl nitrites.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 4 – New Entry

ALKYL NITRITES except those specifically listed elsewhere in these Schedules.

Appendix A – Amend Entry

LUBRICANTS in preparations that provide a lubricating action between machinery parts, except soluble oils and solvent-deposited lubricating agents.

The applicant's reasons for the proposal were:

- There are increasing reports of misuse and abuse of 'poppers' containing short chain volatile alkyl nitrites in the clubbing/dance scene in Australia and globally for the purposes of recreational use alongside narcotics.
- Information received indicates that some suppliers of 'poppers' containing various short chain volatile alkyl nitrites, although not usually amyl nitrite, are claiming that their products are exempt from the Poisons Standard on the basis that they are marketed as 'lubricants'. A lubricating action is unlikely due to the volatility of the alkyl nitrites contained in these products. The products are generally labelled as 'leather cleaners' or 'room odorisers' but there is no credible evidence they are actually used for either of these purposes. Rather the contents of the little bottles are inhaled and cost about \$30 to \$50.
- Ophthalmologists in Australia are reporting an increase in the number of cases of maculopathies (retinal damage) caused by recreational use of 'poppers'/'lubricants' containing alkyl nitrites. These reports have been observed elsewhere in the world, with the first cases reported in *The New England Journal of Medicine* in 2010.
- Proposed amendments to the Poisons Standard include either specific listing of these alternative alkyl nitrites or creating a new entry to ensure clarity of the intent of capturing any volatile alkyl nitrite in Schedule 4.

Current scheduling status

Five (5) alkyl nitrites are listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

AMYL NITRITE.

BUTYL NITRITE.

ISOAMYL NITRITE.

ISOBUTYL NITRITE.

OCTYL NITRITE.

Scheduling history

Amyl nitrite

In January 1955, the Committee of Poisons Schedules placed amyl nitrite in Schedule 3 of the newly created Poisons Standard. In February 1989, following reports of recreational abuse of amyl nitrite and other nitrites a change to Schedule 4 was foreshadowed. Members considered that the substance had no use in contemporary medicine, although anecdotally it was being used by the mining industry as a cyanide antidote. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990.

In November 1993 (deferred from August 1993), the National Drugs and Poisons Committee (NDPSC) considered a proposal to create new Appendix D (Possession of this drug without authority should be illegal) entries for amyl and butyl nitrites owing to their reported use by paedophiles, who administer it to children for anal dilation. The committee decided that due to the lack of precise information about widespread misuse by paedophiles, this proposal was not warranted at this time and that more attention should be paid to policing the illegal supply of a Schedule 4 substance.

In August 1995, the National Drugs and Poisons Committee (NDPSC) considered the use of amyl nitrite as a first-aid treatment for cyanide poisoning. The Committee considered that the use of amyl nitrite as a first aid treatment for cyanide poisoning could not be supported in view of concerns with its safety and efficacy. Consequently, it would not support any change to its current Schedule 4 status. The committee agreed that if amyl nitrite were to be used as an antidote, existing mechanisms were available in each of the States and Territories to permit such use.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for amyl nitrite. At the time the committee noted that amyl nitrite is scheduled in NZ as Part III, but is exempted from scheduling in NZ when sold as an antidote for cyanide poisoning associated with the use of sodium cyanide for vertebrate control. The committee was advised that the Working Party while considering Schedule 4 was appropriate for amyl nitrite recognised the need for an exemption in the NZ entry to allow its availability as an antidote.

Butyl nitrite

In November 1978 a new Schedule 3 entry was created for butyl nitrite, owing to concerns that there were no controls over the substance, which was anecdotally being used as a sex stimulant. In February 1989 an amendment to Schedule 4 was foreshadowed for butyl nitrite and other nitrites. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990.

In November 1993 (deferred from August 1993), the National Drugs and Poisons Committee (NDPSC) considered a proposal to create new Appendix D (Possession of this drug without authority should be illegal) entries for amyl and butyl nitrites owing to their reported use by paedophiles, who administer it to children for anal dilation. The committee decided that due to the lack of precise information about widespread misuse by paedophiles, this proposal was not warranted at this time and that more attention should be paid to policing the illegal supply of a Schedule 4 substance.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Isoamyl nitrite

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Isobutyl nitrite

In February 1989, isobutyl nitrite was among a number of alkyl nitrites being considered for inclusion in Schedule 4 following reports of recreational abuse. A Schedule 4 entry for isobutyl nitrite was created in February 1990.

In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Octyl nitrite

In May 1956 the PSC created a new Schedule 3 entry for octyl nitrite. This scheduling was confirmed for all jurisdictions in February 1985. In February 1989, following reports of recreational abuse of amyl nitrite and other nitrites an amendment to a Schedule 4 entry was foreshadowed. The Schedule 3 entry was deleted and a new Schedule 4 entry created in February 1990. In May 1999, the National Drugs and Poisons Committee (NDPSC) considered harmonisation between Australia and New Zealand for butyl nitrite, octyl nitrite, isoamyl nitrite and isobutyl nitrite. The committee noted that the Working Party did not support adoption of the NZ scheduling for two reasons. In Australia, this group of drugs has been abused with severe adverse effects, and the NDPSC decision to shift the group in Schedule 4 in 1993 was related to reports of administration of nitrites to assist anal penetration in children by paedophiles.

Nitrites

When considering a proposal to delete Schedule 3 entries for amyl, butyl and octyl nitrite and to create new Schedule 4 entries for these substances and also for isobutyl nitrite, the committee decided against making a generic entry for 'ALIPHATIC DERIVATIVES OF NITROUS ACID' as there was a trend away from generic scheduling entries, with specific entries being preferred.

Isopropyl nitrite, Isopentyl nitrite, propyl nitrite, cyclohexyl nitrite

Isopropyl nitrite, Isopentyl nitrite, propyl nitrite and cyclohexyl nitrite are not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Lubricants

Exemptions from scheduling were first proposed at the December 1965 Poisons Schedule Sub-Committee (PSSC) meeting. The original listing was for purposes that in some substances a poison is not likely to be released to cause poisoning. 'Motor fuels and lubricants unless specified in Schedule 5' was first among the first list of exemptions. It was not until the January 1969 PSSC meeting that the recommendation was made to include the list of exemptions, which included 'motor fuels and lubricants'.

Australian regulations

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has no products that contain the alkyl nitrites isopentyl nitrite, 2-pentyl and N-propyl nitrite or cyclohexyl nitrite.

Alkyl nitrites do not appear in the current [Therapeutic Goods \(Permissible Indications\) Determination No. 2 of 2018](#).

According to the [TGA Ingredient Database](#), amyl nitrite, octyl nitrite and nitrite are:

- Available for use as an Active Ingredient in Biologicals, Devices (amyl nitrite only) and Prescription Medicines;
- Available for use as an Excipient Ingredients in Biologicals, Devices and Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

There are no agricultural and veterinary chemicals containing any nitrite listed on the APVMA's [PubCRIS](#).

International regulations

The international legal status of alkyl nitrites is unclear. In the European Union (EU), isobutyl nitrite was classified as a class 2 carcinogen under the EU Directive 76/769/EEC, making it illegal for shops to sell this variety of poppers.

In January 2016, the United Kingdom (UK) government included alkyl nitrites in a list of banned psychoactive substances, but this decision was set to be reviewed, and it is unclear whether this decision remains.

In New Zealand (NZ), amyl nitrite is a prescription medicine **except** when sold to a person who holds a controlled substances licence (issued under section 95B of the *Hazardous Substances and New Organisms Act 1996*) authorising the person to possess cyanide and **except** when sold to an exempt laboratory covered by a *Hazardous Substances and New Organisms Act 1996* approved code of practice. Octyl nitrite, isobutyl nitrite, butyl nitrite and isoamyl nitrite are classified as prescription medicines.

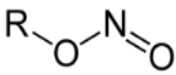
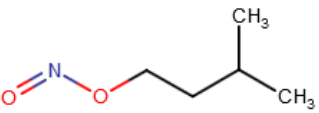
Substance summary

'Poppers' is the street term for various alkyl nitrites taken for recreational purposes through direct inhalation. In the past these included amyl nitrite, butyl nitrite and isobutyl nitrite, with more recent variations including isopropyl and cyclohexyl nitrite. Alkyl nitrites have a smooth muscle relaxant effect, and were first used therapeutically (amyl nitrite) to treat angina. They have been used as recreational drug for the reported sensations of head rush, euphoria, uncontrollable laughter or giggling, and other sensations that result from the hypotensive effect and increase sexual arousal and desire. In addition, the smooth muscles of the anus and vagina are relaxed. Adverse effects of short term use include severe headache, throat irritation, nose bleeds, nausea, erectile problems, sensations of spinning or falling and dyspnoea. According to St George's Hospital, University of London, there have been 14 deaths in the UK related to inhaling alkyl nitrites since 1971, three of which were in 2006.³⁰

In Australia, the drugs are sold under the guise of room deodorisers and cleaning solvents, and are readily available in adult shops and online. National Drug and Alcohol Research Centre's (NDARC) Ecstasy and Related Drugs Reporting System (EDRS) shows use of amyl nitrite (and may include other alkyl nitrites) running at 27% of those who participated in the survey in 2016 (up from 21% in 2015).³¹ The demographics of the survey group suggest popper use has expanded to the community more generally – it was once associated more with the lesbian, gay, bisexual, trans, and/or intersex (LGBTI) community.

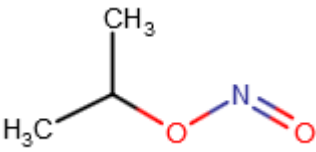
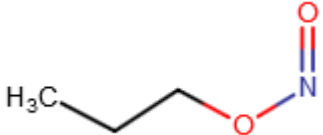
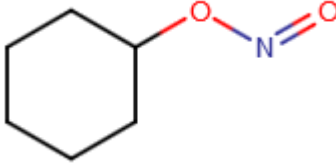
Ophthalmologists in Australia are seeing an increase in cases of temporary and permanent macula damage caused by recreational drug use of alkyl nitrite compounds. Ophthalmologists believe that chronic use could lead to irreversible damage. Alkyl nitrite 'popper' maculopathy causes gradual vision loss and clinically is the equivalent of having a hole burned in the macula from gazing at the sun.

Table 1.3: Chemical information for volatile alkyl nitrites

Chemical	CAS number	IUPAC and/or common and/or other names	Molecular formula and weight	Chemical structure
General information for volatile alkyl nitrites	N/A	N/A	R-NO ₂	
Amyl nitrite	110-46-3	3-Methylbutanol nitrite; isoamyl nitrite; nitrous acid, 3-methylbutyl ester; nitrous acid, isopentyl ester	C ₅ H ₁₁ NO ₂ 117.1 g/mol	

³⁰ <http://www.re-solv.org/wp-content/uploads/2011/12/Poppers.pdf>

³¹ Stafford J and Breen J (2016) 'Trends in ecstasy and related drug markets', *Australian Drug Trends Series No. 172*

Chemical	CAS number	IUPAC and/or common and/or other names	Molecular formula and weight	Chemical structure
Isopropyl nitrite	541-42-4	2-Propanol nitrite; isopropylester kyseliny dusite; nitrous acid, 1-methylethyl ester	C ₃ H ₇ NO ₂ 89.1 g/mol	
N-Propyl nitrite	543-67-9	Nitrous acid, n-propyl ester; propanol nitrite; propyl nitrite	C ₃ H ₇ NO ₂ 89.1 g/mol	
Cyclohexyl nitrite	5156-40-1	Nitrous acid, cyclohexyl ester; N-cyclohexyl nitrite; cyclohexyl alcohol nitrite; C-hexyl nitrite; O-nitrosocyclohexanol	C ₆ H ₁₁ NO ₂ 129.2 g/mol	

Pre-meeting public submissions

Three (3) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. Two (2) submissions were in support of the proposed amendments, and one (1) was in conditional support.

The main points provided in support of the amendment were:

- Alkyl nitrites have a minimal therapeutic role:
 - Volatile nitrites (such as amyl nitrites) are no longer used as a first aid measure to induce methaemoglobinaemia after cyanide exposure. Current alternative treatment recommendations for this indication include sodium thiosulfate plus hydroxocobalamin, or sodium nitrite plus sodium thiosulfate.³²
 - There is limited support for a Schedule 4 entry for alkyl nitrites to allow them to be used in cyanide antidote kits under the Special Access Scheme only.
 - Volatile nitrites were historically used to treat angina. However, they have been replaced by nitrates.

³² Therapeutic Guidelines, Toxicology and Wilderness, Therapeutic Guidelines Ltd (eTG March 2018 edition)

- Abuse potential:
 - Evidence provided by poisons information centres (PIC) around Australia indicate increasing misuse and harms.
 - PIC data indicates that alkyl nitrites are often used as party drugs.
 - PIC data indicates alkyl nitrites are used at home recreationally for their euphoric properties and as sex aids.
 - To avoid detection by authorities, alkyl nitrites are often labelled and sold as leather cleaner, video head cleaner, incense or room-odorising products. This can result in misidentification and impair the risk assessment.
- Alkyl nitrites toxicity:
 - Toxicity of alkyl nitrites is primary due to vasodilatory actions. This includes tachycardia, hypotension, headache, flushing, dizziness, nausea, and syncope.³³
 - Methaemoglobinaemia is a relatively uncommon but potentially life threatening consequence of alkyl nitrite exposure.³⁴

The main points provided in conditional support of the amendment were:

- A Schedule 4 entry with an associated Appendix D entry for alkyl nitrites would be more appropriate than just a Schedule 4 entry. However, a Schedule 9 or Schedule 10 entry is preferred due to lack of therapeutic use, abuse potential and significant harms.

ACMS advice

The committee made the following recommendations:

1. that the Appendix A entry for LUBRICANTS be amended as follows:

Appendix A – Amend Entry

LUBRICANTS **in preparations that provide a lubricating action between machinery parts, except** soluble oils and solvent-deposited lubricating agents.

2. that new Schedule 9 entries for alkyl nitrites, isopropyl nitrite, propyl nitrite and cyclohexane nitrite be created as follows:

Schedule 9 – New Entries

ALKYL NITRITES except those specifically listed elsewhere in these Schedules.

ISOPROPYL NITRITE.

PROPYL NITRITE.

CYCLOHEXANE NITRITE.

³³ Romanelli, F. *et al.*, 2004. Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse. *Pharmacotherapy*, 24(1), pp.69–78

³⁴ Hunter, L. *et al.*, 2011. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: A review. *British Journal of Clinical Pharmacology*, 72(1), pp.18–26.

3. that amyl nitrite, butyl nitrite, isoamyl nitrite, isobutyl nitrite and octyl nitrite be up-scheduled from Schedule 4 to Schedule 9 as follows:

Schedule 9 – New Entries moved from Schedule 4

AMYL NITRITE.

BUTYL NITRITE.

ISOAMYL NITRITE.

ISOBUTYL NITRITE.

OCTYL NITRITE.

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

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

The reasons for the advice included:

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

- Numerous risks of harms with little or no therapeutic benefit.
- No benefits except possibly for the use of amyl nitrite as alternative antidote for cyanide poisoning if IV access or first line antidote not immediately available.
- Risks include illicit use for euphoric and muscle relaxant effects, adverse events including maculopathy and methaemoglobinaemia.

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

- Alkyl nitrites have little to no therapeutic use. Limited and superseded therapeutic use for amyl nitrite only, which is included in Schedule 4.
- Largely recreational use as a ‘party drug’.
- No medicinal use.

(c) the toxicity of a substance:

- Via inhalation includes tachycardia, hypotension, headache, flushing, dizziness, nausea, and syncope. Combination with other drugs like sildenafil can lead to severe hypotension.
- Chemical burns to the skin and eyes on direct contact.
- Can lead to methaemoglobinaemia via inhalation with significantly increased risk if ingested.
- Can cause death – Methaemoglobinaemia can occur and is potentially life threatening if not treated appropriately. Fatalities have been recorded.
- Other risks include maculopathy and skin lesions.
- Also increased risk of cardiovascular harm when used in conjunction with other vasodilators such as sildenafil.

(e) the potential for abuse of a substance:

- High potential for abuse for euphoric properties and as sex aids.
- High risk of misuse and abuse – but tends to be in particular sections of the community rather than widespread use.

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

- Appendix A entry to clarify the meaning of lubricants under the SUSMP to manage the risk associated with the use of alkyl nitrites found in 'poppers'.

1.4 Codeine

Delegate's interim decision

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

Reasons:

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

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

- Codeine is considered a weak opioid analgesic and antitussive. Risks include dependence, and harms associated with taking large quantities of combination analgesic products, predominantly in the context of over the counter (OTC) use.
- As noted in the recent up-scheduling of codeine there is little evidence of efficacy at low doses (8-15 mg) so reducing the Schedule 4 dose to 12 mg is not appropriate.

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

- Predominantly analgesia, with some use as an antitussive. As an analgesic codeine combination is widely used, for example over 12 million packets of Schedule 4 codeine products were sold in Australia in 2013.

(c) the toxicity of a substance:

- Codeine is considered a weak opioid, there is the potential for toxicity with rapid metabolisers otherwise, codeine is considered to have lower potency compared with other opioids.³⁵

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

- Combination products with up to 30 mg in a dose unit, compounded with another active ingredient. Formulations with codeine as a single ingredient are Schedule 8.

(e) the potential for abuse of a substance:

- Codeine is a weak opioid analgesic. There is evidence of non-medical use and dependence with combination codeine products, though this evidence was generated during the period of time when codeine was widely available in an over-the-counter medication. Blinded abuse liability studies indicate that doses of 100 mg of codeine have a placebo like effects on abuse liability while higher doses (200 mg) were similar to tramadol and oxycodone in their abuse liability)above.³⁵ This suggests that in a controlled blinded clinical trial a therapeutic dose of 60mg (2 x 30 mg codeine + 500 mg paracetamol) has lower abuse liability than therapeutic doses of tramadol or oxycodone.

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

- Given the recent rescheduling of codeine to delete the Schedule 3 entry was only implemented in February 2018, there is minimal experience and data to inform if additional regulatory measures are required.

³⁵ Babalonis S, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL. Abuse Liability and Reinforcing Efficacy of Oral Tramadol in Humans. Drug and alcohol dependence. 2013;129(1-2):116-124. doi:10.1016/j.drugalcdep.2012.09.018.

- Reporting systems currently in use, as well as those proposed for roll out in the coming months, already have the capability to capture Schedule 4 medicines such as codeine at the discretion of the jurisdictions.
- The current scheduling of codeine as a prescription only medicine is now in alignment with many comparable international regulators.
- Due to significant use of S4 codeine combination products there does not appear to be substantive evidence of significant diversion and abuse of combination codeine (more than 12 mg) analgesics in institutional healthcare to warrant the additional security and accountability measures a Schedule 8 status affords.
- The significant economic and administrative burden of meeting the storage, distribution, supply and record keeping requirements for Schedule 8 medicines will increase costs which sponsors may not be able to absorb. This could impact product viability creating an access barrier to effective pain relief for patients.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to codeine;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- 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 was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for codeine

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to codeine. The application proposed to amend the Schedule 4 and Schedule 8 entries for codeine.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 4 – Amend Entry

CODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing ~~30~~12 mg or less of codeine per dosage unit; or
- b) in undivided preparations containing ~~1~~0.25 per cent or less of codeine.

Schedule 8 – Amend Entry

CODEINE ~~alone or when compounded with one or more other therapeutically active substances:~~

- a) ~~in divided preparations containing more than 12 mg of codeine per dosage unit; or~~
- b) ~~in undivided preparations containing more than 0.25 per cent of codeine;~~

except when included in Schedule 4.

The applicant's reasons for the proposal were:

- The application seeks to address scheduling inconsistencies highlighted in the [Regulation Impact Statement \(RIS\)](#). This will be achieved by moving high dose codeine-containing medicines and single ingredient 30 mg codeine into Schedule 8 where, as suggested by the RIS, these products belong.
- By up-scheduling high dose codeine-containing medicines to Schedule 8, they will be monitored by State and Territory Real Time Monitoring systems such as DORA in Tasmania or SafeScript, soon to be implemented in Victoria. As the Victorian system will address system insufficiencies of the DORA platform it will easily be implemented in other states and territories with the assistance of funds recently announced by Minister Hunt.

Current scheduling status

Codeine is listed in Schedules 4 and 8 and Appendix K of the Poisons Standard as follows:

Schedule 4

CODEINE when compounded with one or more other therapeutically active substances:

- a. in divided preparations containing 30 mg or less of codeine per dosage unit; or
- b. in undivided preparations containing 1 per cent or less of codeine.

Schedule 8

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

Appendix K

CODEINE.

Scheduling history

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

The NDPSC agreed to form a Codeine Working Party to review the availability of all over the counter (OTC) combination analgesics containing codeine. This followed concerns raised at previous NDPSC meetings (June 2005, October 2005 and June 2007) of abuse of codeine from a codeine-ibuprofen combination analgesic product (by cutting a bi-layer tablet in half to access the codeine, or separating codeine from the product by simple dissolution in water).

NDPSC: February 2009

The NDPSC considered a report from the Codeine Working Party, together with findings from an evaluation of OTC codeine-containing analgesics, and agreed to foreshadow a proposal to re-schedule all OTC codeine to Schedule 3 (with suggestions to limit the maximum daily dose to 100 mg codeine, limit the maximum pack size to 5 days' supply, restrict divided preparations to 12 mg of codeine per dosage unit and restrict undivided preparations to 0.25% codeine). In addition, a member proposed to maintain a Schedule 2 entry for codeine with phenylephrine, if all other OTC codeine was included in Schedule 3. The NDPSC foreshadowed a proposal to include all OTC codeine (and not just analgesics) to encourage public comment.

NDPSC: June 2009

The NDPSC agreed that the current scheduling of OTC codeine combinations for coughs and colds remained appropriate (but with a pack size limit of 5 days' supply), and that all OTC combination analgesics containing codeine should be re-scheduled from Schedule 2 to Schedule 3 (with the maximum daily dose limited to 100 mg, the duration of treatment limited to 5 days, divided preparations restricted to 12 mg of codeine per dosage unit and undivided preparations restricted to 0.25% codeine) and that Schedule 3 codeine should not be included in Appendix H. The implementation date was to be 1 May 2010.

NDPSC: October 2009

Following consideration of June 2009 post-meeting submissions and further discussion, the NDPSC agreed to amend the pack size limit for Schedule 2 cough and cold preparations to a maximum of 6 days' supply. The NDPSC also confirmed the June 2009 resolution regarding the Schedule 3 entry for all OTC combination analgesics containing codeine. The implementation date remained as 1 May 2010. An editorial amendment was made to the Schedule 3 entry at the February 2010 NDPSC meeting.

Advisory Committee on Medicines Scheduling (ACMS): June 2011

The scheduling of codeine was considered as a part of the cold and cough preparation review, which looked at the use of these preparations for the treatment of children aged 2 to 12 years. Taking into consideration the advice from the ACMS, the delegate decided that there should be no change to the scheduling of codeine in cold and cough preparations.

ACMS: August 2015

The ACMS considered a proposal to re-schedule codeine with assistance from an independent external evaluation, public submissions and the original application. Consideration was given as to whether all current Schedule 3 preparations should be rescheduled to Schedule 4, or whether any rescheduling to Schedule 4 should only apply to combination analgesic products containing codeine. Consideration was also given to whether the Schedule 2 entry for codeine should be amended. The committee recommended that the Schedule 2 and Schedule 3 entries for codeine be deleted and that the Schedule 4 and Schedule 8 entries be amended to reflect this.

Delegate's Decision: November 2015

The delegate announced that a decision on the re-scheduling of codeine would be delayed to allow a more thorough consideration of the numerous submissions received from the pre-meeting and interim decision consultation periods and the broader implications to the then current products in the market.

Call for further submissions: December 2015

A notice was published on the TGA website calling for further submissions from interested parties on the proposed re-scheduling options for codeine. This call for further submissions was based on feedback received during the consultation periods.

Advisory Committee on the Safety of Medicines (ACSOM): March 2016

The ASCOM provided advice on products containing low dose codeine (8-15 mg codeine or codeine phosphate) that were available as a Schedule 2 and Schedule 3 medicine. The committee noted that the OTC availability of codeine-containing medicines supported a general misconception in the community that codeine is safe. It was also noted that there would need to be additional measures, such as education and possible up-scheduling, to achieve the desired outcome to reduce the risks associated with codeine.

ACMS: March 2016

The ACMS again considered the proposal to re-schedule codeine. The ACMS advised that their recommendation to up-schedule codeine from Schedule 2 and 3 to Schedule 4 from the August 2015 remains the same. The delegate agreed and made a final decision to up-schedule all medicines containing codeine to be Schedule 4 Prescription Only Medicines. This was published on the TGA website, along with the KPMG report and the RIS. As part of the final decision, an implementation date of 1 February 2018 was announced by the delegate, which provided more than a year for implementation. This balanced the needs of affected stakeholders while addressing the harms associated with these products.

Australian regulations

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has 207 products that contain codeine, codeine phosphate hemihydrate or codeine phosphate sesquihydrate.

In the last 30 years there have been 1670 reported cases of adverse events related to codeine in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 634 cases with a single suspected medicine and 103 cases where death was the reported outcome.

According to the [TGA Ingredient Database](#), codeine is:

- Available for use as an Active Ingredient in: Biologicals, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

According to the [TGA Ingredient Database](#), codeine phosphate hemihydrate is:

- Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Export Only, Over the Counter, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

According to the [TGA Ingredient Database](#), codeine phosphate sesquihydrate is:

- Available for use as an Active Ingredient in: Biologicals, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

International regulations

Countries in Europe including Austria, Belgium, Germany and Italy, as well as the United States, Japan, Russia and the United Arab Emirates all require prescriptions for medicines containing codeine. In some other countries, including Hong Kong, Hungary and the Netherlands, OTC sale of cough linctus (containing codeine) is allowed, with all other medicines containing codeine requiring a prescription.

In July 2017, the new French Government announced that all medicines containing codeine would only be available via prescription.

In November 2017, Canada completed a public consultation on making codeine products Prescription Only.

In November 2017, Medsafe New Zealand made their recommendation that, from 31 January 2020, all codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified to prescription medicines with a proposed exception applying to medicines containing not more than 15 mg of codeine per unit, with a maximum daily dose not exceeding 90 mg of codeine for use as an analgesic and when sold in a pack of not more than three day's supply. Medsafe is also advocating for a national monitoring of all codeine-containing medicines, including restricted and prescription, subsidised and unsubsidised medicines.

In January 2018, the Kenya Pharmacy and Poisons Board (KPPB) announced that all medicines that contain codeine have been rescheduled from Pharmacy Only Medicines to Prescription Only Medicines in an effort to minimise the risk of overuse and addiction. In addition, the KPPB have given all marketing authorisation holders six months to change packages to include clear and prominently positioned warnings on the label.

Substance summary

Codeine and its salts, especially codeine phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. Codeine phosphate is also given by intramuscular injection for the relief of pain, in doses similar to those used orally; the intravenous, subcutaneous, and rectal routes have also been used.

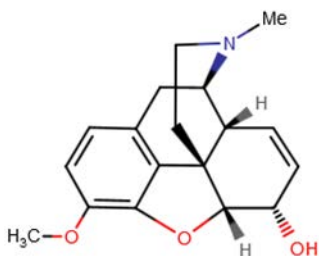
For the relief of pain, codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive cough, codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of acute diarrhoea in doses of 15 to 60 mg given three to four times daily.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonate diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparation.

Table 1.4: Chemical information of codeine

Property	Codeine
CAS number	76-57-3
IUPAC and/or common and/or other names	Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5- α ,6- α)- (9CI); methylmorphine; codeine phosphate; codeine anhydrous; morphine monomethyl ether.
Chemical structure	
Molecular formula	C ₁₈ H ₂₁ NO ₃
Molecular weight	299.4 g/mol

Pre-meeting public submissions

Nine (9) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. Two (2) submissions were in support and seven (7) opposed to the proposed amendments.

The main points provided in support of the amendment were:

- There is evidence of codeine medicines being associated with adverse health risks.³⁶
- Further restricting access to sub-therapeutic doses of codeine is consistent with the Choosing Wisely Australia recommendation advising against the use of low-dose codeine.
- As federal and jurisdictional governments continually invest in real-time prescription monitoring systems which focus strongly on Schedule 8 medicines, this up-scheduling would empower clinicians to appropriately monitor codeine prescribing and supply to ensure optimal and safe patient care.

The main points provided in opposition of the amendment were:

- The up-scheduling of Schedule 3 codeine to Schedule 4 on 1 February 2018 adequately addressed the inconsistencies in codeine scheduling. Further, there is no new evidence supporting additional up-scheduling.
- Australia's codeine scheduling status is now in alignment with many other countries. No other country classifies codeine as a 'Controlled Substance (Schedule 8)' or equivalent. Further restricting products containing more than 12 mg of codeine to Schedule 8 will remove the international alignment Australia has recently achieved.
- Both Schedule 4 and 8 products are prescription only medicines, requiring the clinical assessment of a medical practitioner and dispensing by a pharmacist. This presents further opportunity to clinically evaluate the appropriateness of the supply. The recent up-scheduling of all over the counter codeine products to prescription only and the potential for all codeine supplies to be included in real-time prescription monitoring systems provides significant and sufficient safeguards for patients in the community.
- There does not appear to be substantive evidence of significant diversion and abuse of combination codeine (more than 12 mg) analgesics in institutional healthcare to warrant the additional security and accountability measures a Schedule 8 status affords.
- The risk to patient safety was mitigated through consideration of formulation (single active ingredient only versus combination), the amount of codeine per dosage unit and total amount of codeine per pack. The single ingredient products remain in Schedule 8 and combination products containing codeine when compounded with one or more other therapeutically active substances are in Schedule 4.
- The distinction between codeine being used as a single active ingredient or compounded in a divided preparation product provides a degree of mitigation of risk and is adopted for other substances.

³⁶ TGA. (2018). [Codeine information hub: Codeine use can be harmful](#) and Shaheed, C. A., Maher, C. G., & McLachlan, A. (2016). Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine based antitussives.

- The significant economic and administrative burden of meeting the storage, distribution, supply and record keeping requirements for Schedule 8 medicines will increase costs which sponsors may not be able to absorb. This could impact product viability creating an access barrier to effective pain relief for patients.
- Storage of Schedule 8 medicines:
 - Schedule 8 medications carry significantly greater requirements for secure storage, chain of custody and record keeping due to the potential for diversion and abuse through the supply chain.
 - The stringent controls and record keeping required to manage the storage, distribution and supply of Schedule 8 goods will warrant significant investment in infrastructure and logistics considering the product volumes, which in turn will increase the cost of goods and potentially impact product viability.
 - The increased cost burden will need to cover vault storage requirements, additional vigilance on picking and inventory validation activities as well as higher costs of a premium freight service. These additional costs incurred via wholesale channels may further impact the product price point and potentially patient access. The additional financial costs will also impact numerous parts of the medicine supply chain including wholesalers, pharmacies, aged care facilities, consumers and the Commonwealth through increased Controlled Drug dispensing fees.
 - One submission outlined that in excess of \$1.5 million would be required to expand their current Schedule 8 storage facilities. This expense would have significant impact on the cost of the goods and would likely result in product discontinuation.
 - As current storage facilities are insufficient this would result in stock shortages.
 - Previous experience with up-scheduling a product to Schedule 8 saw a more than 50% decline in sales. This was not attributed to lack of need but rather to the preferred ease of prescribing a Schedule 4 medicine.
 - Pharmacies must store Schedule 8 medicines in a Controlled Drug safe that meets jurisdictional requirements. Such medicine safes have a limited storage capacity and with more Schedule 8 medicines being prescribed, pharmacies must assess and resolve the storage requirements. Replacing a safe or installing an additional one can be costly, and some pharmacies may not have the space for such measures without a significant refit of the dispensary.
 - The additional legislative requirements regarding Schedule 8 medicine storage receptacles are likely to be problematic for many health services if they are faced with also including these high volume codeine combination products in existing safes. Overcrowding of existing Schedule 8 safes to accommodate the additional products (in high volumes in some instances) may potentially lead to unintended negative patient outcomes relating to medication selection errors, a known risk with other higher potency Schedule 8 opioids.
- Additional security and accountability measures will ultimately detract from available time to deliver existing healthcare services to patients in need.
 - The proposed re-scheduling will have a negative impact on health professional productivity and physical work environments within institutional healthcare settings which would result from the additional regulatory and administrative burden.

- An additional estimated 28,000 transactions per annum would need to be recorded by pharmacists through controlled drug registers for predominantly hospital and residential care supplies. There would also be flow-on transactional requirements for nursing staff within the health care facilities. Additionally, there would also be more time taken to periodically count and reconcile register and physical stock balances.
- Acute care and aged care facilities will be significantly affected with facilities requiring extra security for the storage of the additional Schedule 8 medicines as well as the administrative burden for staff in storing, handling, administering and recording.
- Schedule 8 medicines will require a separate prescription thereby affecting the National Residential Medication Chart.
- The simulation and modelling conducted for the RIS for the low dose codeine rescheduling scenarios do not apply to higher dose codeine medicines and further up-scheduling was not included as part of the RIS recommendations. In particular, the significant economic impacts of managing the supply of Schedule 8 medicines, due to the strict storage, distribution and record keeping requirements, represents a completely different set of scenarios to those considered in the previous RIS and requires a new assessment.
- Sponsors may cancel their products as a result of the up-scheduling. The use of alternative prescription medicines are likely to increase which may result in the manufacturers not being able to meet demand and patients being unable to readily access alternative analgesics.
- Real time reporting:
 - Codeine medicines should be subject to Real Time Monitoring and it is unnecessary to up-schedule to Schedule 8 for this to occur.
 - The Tasmanian Drugs and Poisons Information System Online Remote Access (DORA) currently considers codeine as a relevant substance for real-time reporting, and Schedule 4 codeine is expected to be included in SafeScript in Victoria.
 - The COAG Health Council announced³⁷ that federal, state and territory Health Ministers agreed to progress national real time prescription monitoring as a federated model with jurisdictions committed to progressing development and adaptation of systems to connect to and interface with Commonwealth systems to achieve a national solution.
- The Medicines Classification Committee in New Zealand have proposed to down schedule codeine as a single ingredient for sale over the counter from 31 January 2020.³⁸ Down-scheduling codeine from Schedule 8 to Schedule 4 may address the inconsistencies with codeine.
- One submission proposed to amend the Schedule 8 entry to include divided preparations containing more than 30 mg of codeine per dosage unit and in undivided preparations containing more than 1 per cent of codeine.

³⁷ [COAG Health Council Communique 13 April 2018](#)

³⁸ [Minutes of the 59th meeting of the Medicines Classification Committee held in Wellington on Tuesday 7 November 2017](#)

ACMS advice

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

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

The reasons for the advice included:

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

- Codeine is considered a weak opioid analgesic and antitussive. Risks include dependence, and harms associated with taking large quantities of combination analgesic products, predominantly in the context of OTC use.

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

- Predominantly analgesia, with some use as an antitussive. As an analgesic codeine combination is widely used, for example over 12 million packets of S4 codeine products were sold in Australia in 2013.

(c) the toxicity of a substance:

- Codeine is considered a weak opioid, there is the potential for toxicity with rapid metabolisers otherwise, codeine is considered to have lower potency compared with other opioids.³⁵

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

- Combination products with up to 30mg in a dose unit, compounded with another active ingredient. Formulations with codeine as a single ingredient are Schedule 8.

(e) the potential for abuse of a substance:

- Codeine is a weak opioid analgesic. There is evidence of non-medical use and dependence with combination codeine products, though this evidence was generated during the period of time when codeine was widely available in an over-the-counter medication. Blinded abuse liability studies indicate that doses of 100mg of codeine have a placebo like effects on abuse liability while higher doses (200mg) were similar to tramadol and oxycodone in their abuse liability)above.³⁵ This suggests that in a controlled blinded clinical trial a therapeutic dose of 60mg (2 x 30mg codeine + 500mg paracetamol) has lower abuse liability than therapeutic doses of tramadol or oxycodone.

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

- Given the recent rescheduling of codeine to delete the Schedule 3 entry, there is minimal experience and data to inform if additional regulatory measures are required.

1.5 Cannabidiol and tetrahydrocannabinols (THCs)

Delegate's interim decision

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

Reasons:

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

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

- There is no additional information provided on the risks and benefits of tetrahydrocannabinol (THC) or other non-cannabidiol cannabinoids to justify their down-scheduling.
- Cannabidiol is not psychoactive however THC and selected other cannabinoids are psychoactive.
- No evidence has been provided to show that THC concentrations up to 1% are safe and have no psychotropic effects at this concentration.
- Cannabinoids may have benefits in a range of indications.

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

- Cannabis is an experimental drug and its down-scheduling from Schedule 9 to Schedule 8 already facilitates experimental therapeutic use. Further down-scheduling of cannabinoids is inappropriate at this time until adequate data is provided proving safety and efficacy. There is no evidence that the Schedule 8 classification of cannabis products other than cannabidiol is a significant barrier to appropriate prescribing and use.

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

- There are a diverse range of formulations being developed containing a range of cannabinoid concentrations.
- The Schedule 4 entry for cannabidiol needs to define products for which the cannabidiol is the predominant active compound and as such is likely to limit the ability to consume psychoactive THC doses from that product.
- The recent final decision from the March 2018 ACMS meeting amends the cannabidiol Schedule 4 entry to further clarify the intent of the concentration limits of cannabidiol in relation to total other cannabinoids. This is:

§ CANNABIDIOL in preparations for therapeutic use where:

- * cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and
- * any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and total 2 per cent or less of the cannabinoid content of the preparation.

(e) the potential for abuse of a substance:

- Cannabis and its preparations and especially products containing THC are subject to abuse.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to cannabidiol and tetrahydrocannabinols;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- 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 purpose for which a substance is to be used and the extent of use; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for cannabidiol and tetrahydrocannabinols

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to cannabidiol and tetrahydrocannabinols (THCs). The application proposed to amend the Schedule 4 entry for cannabidiol.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 4 – Amend Entry

CANNABIDIOL in preparations for therapeutic use ~~containing 2 per cent or less of~~ where other cannabinoids found in cannabis **comprise no more than 1% w/v of the product.**

The applicant's reasons for the proposal were:

- The applicant was advised by the WA Health Department that one of their products would come under Schedule 8 ('unless 98% of the total cannabinoids in the preparation are cannabidiol, it is in Schedule 8. In other words, the total amount of cannabinoids that are not cannabidiol would need to be 1:50 before the preparation would meet the Schedule 4 entry').
- The applicant argues that the decision to classify the product is erroneous since it compares the strength of one ingredient to another which is flawed. Classifying by using absolute weight per volume (%w/v) is the standard method of rating pharmaceutical strength and gives a true indication of the amount of THC. The product (1 mg THC/mL) contains low levels of THC. To classify it in the same schedule as the much higher strengths of 10 mg THC/mL and 18 mg THC/mL is confusing to prescribers.

- The application is based on the low harm/misuse potential of medicinal cannabis products and of the erroneous current scheduling classification comparing one cannabinoid to another rather than by %w/v (of the product).
- This scheduling application is in the public interest. Medicinal cannabis prescriptions are monitored closely by the TGA. Each prescription requires approval via the Special Access Scheme (SAS) category B. In some cases, further state approval may be needed. All applications are subject to a series of patient monitoring and after care. There are 3 strengths of this medication, the other two are Schedule 8 and re-classification is sought of the weakest strength to Schedule 4.
- There is an extremely low risk of overdosing on the product oil due to the provision of an accurate volumetric measuring device and clear dosing instructions. Furthermore, it should be noted that this extremely low risk would be the same with a 1:50 oil, which would be included in Schedule 4 based on its relative concentration of cannabinoids. Compared to the 1:20 oil, it would have the same concentration of THC and a higher CBD concentration (50 mg/mL).
- The risk of diversion for recreational use is insignificant with the product based on:
 - Inability to concentrate the product;
 - The olive oil carrier cannot be smoked or vaporised;
 - The amount of oil that would need to be ingested to get any possible recreational effect is clearly unattractive;
 - The total amount of 60 mg of THC per bottle of the product oil is below typical amounts ingested by recreational users;
 - CBD is a THC agonist and would moderate any effect; and
 - Oral or sublingual THC gives lower blood levels over a longer period compared to smoked cannabis.
- Compared with other products legally available in Australia (including the 18:0 and 10:10 oils), the product oil 1:20 is an unreasonably expensive and clearly unattractive option to access THC for recreational purposes. The current retail price of the product is \$350 per 60 mL bottle.
- Under the federal TGA system [TGO93](#): (9)

'...are taken to be active ingredients for the purposes of this order (whether or not those ingredients are specified, disclosed, purported or notified to the Secretary to be active ingredients):

(a) any tetrahydrocannabinol present in a medicinal cannabis product, the quantity or proportion of which (together with any corresponding acid) is greater than or equal to 1.0% w/w or w/v of the product'
- Interpreting the THC content in the three product oils based on the above information:
 - The 1:20 oil: 1.0 mg/mL, hence 0.1 % w/v THC should be in Schedule 4 (contains 20.0 mg/mL CBD or 2.0 % w/v, hence regarded as CBD);
 - The 10:10 oil: 9.8 mg/mL, hence 1.0 % w/v THC due to rounding (closer than 0.9 %) should be in Schedule 8; and
 - The 18:1 oil: 18.3 mg/mL, hence 1.8 % w/v THC should be in Schedule 8.

- Using an absolute limit on other cannabinoids in cannabidiol preparations is more appropriate from a patient safety perspective. It will limit psychotropic amounts of THC in a final preparation, which the current scheduling does not.

Current scheduling status

Cannabidiol

Cannabidiol is specifically listed in Schedules 4 and 8 of the Poisons Standard as follows:

Schedule 4

CANNABIDIOL in preparations for therapeutic use containing 2 per cent or less of total other cannabinoids found in cannabis.

Schedule 8

NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidiavarol, 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.

Index

CANNABIDIOL

cross reference: CANNABIS, NABIXIMOLS

Schedule 4

THC

THC is specifically listed in Schedules 8 and 9 and Appendices D and K of the Poisons Standard as follows:

Schedule 8

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

- a) included in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or
- b) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or
- c) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,

except when:

- i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the Therapeutic Goods Regulations 1990 applies; or
- ii) separately specified in the NABIXIMOLS entry in this Schedule.

Schedule 9

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

- a) when included in Schedule 4 or Schedule 8; or
- b) processed hemp fibre containing 0.1 per cent or less of tetrahydrocannabinols, and hemp fibre products manufactured from such fibre; or
- c) in hemp seed oil for purposes other than internal human use containing 50 mg/kg or less of total cannabinoids, including 20 mg/kg or less of tetrahydrocannabinols, when labelled with either of the following warning statements:
 - i) Not for internal use; or
 - ii) Not to be taken.

Appendix D, Item 1

TETRAHYDROCANNABINOLS for human use.

Appendix K

TETRAHYDROCANNABINOLS

Scheduling history

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 nabiximols, which lead 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 the nabiximols product which contains both THC and CBD. It was noted that it was difficult to give approval to special access scheme 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, following further research regarding the nabiximols product, the NDPSC decided that a Schedule 8 entry needed to exempt only the formulation from Schedule 9 rather than the 'substance' and therefore created the Schedule 8 entry for *Cannabis sativa* extract, listing the individual cannabidiols and restricting its presentation to buccal sprays for therapeutic use.

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 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 Chemicals Scheduling-ACMS 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 THC's and the Appendix K entries of cannabis and THC's to clarify the meaning of the cannabidiol Schedule 4 entry. The decision on this proposal is still pending.

Australian regulations

On the [Australian Register of Therapeutic Goods \(ARTG\)](#), there is one product containing cannabidiol for export only, and no products THC.

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 THC.

In the last 30 years, in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#) there have been no reported cases of adverse events related to cannabidiol or THC.

International regulations

- **New Zealand:** Cannabidiol is classified as a Class B1 Controlled drug and Prescription Medicine and THC is classified as a Class C1 Controlled Drugs.
- **United States of America (USA):** In the USA, 13 states have statutes recognising CBD for medical use, 23 states have statutes recognising 'medicinal marijuana'
- **European Union:** The European Medicines Agency approved CBD for certain medical uses (GvHD, Dravet syndrome, Lennox-Gastaut syndrome, perinatal asphyxia) and THC for the treatment of pain and spasticity.
- **Canada:** Cannabidiol and THC are classified as a Schedule II medicine.

Substance summary

Cannabis

Cannabis is a term used to describe a range of varieties of the *Cannabis* genus. The Cannabis plant produces a resin containing compounds called cannabinoids. Some cannabinoids possess psychoactive properties.

Cannabis contains about 60 cannabinoids, of which the main active constituent is delta-9-tetrahydrocannabinol. Delta-9-tetrahydrocannabinol reportedly has anti-emetic properties, and has been associated with claims relating to use for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetics. Another active cannabinoid present in Cannabis is cannabidiol, which is associated with claims relating to use as an analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic.

Nabiximols is a specific extract of *Cannabis sativa* which contains a range of cannabinoids, of which THC 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 as an adjunctive treatment for the symptomatic relief of neuropathic pain associated with multiple sclerosis in adults.

Nabilone is a synthetic cannabinoid used as an anti-emetic in the treatment of nausea and vomiting caused by chemotherapy and also for patients who are not responsive to conventional anti-emetic treatments.

Hemp seed oil as defined in Part 1 Interpretation, Paragraph (1) of the Poisons Standard is the oil obtained by cold expression from the ripened fruits (seeds) of *Cannabis sativa*. Hemp oil is distinct from hemp seed oil and includes extracts from the flowering tops or leaves or any other part of the Cannabis plant other than the ripened fruit (seeds).

Information in the public domain, including websites and literature articles³⁹ report cannabinoids are not synthesised within the hemp seed. However, traces of delta-9-tetrahydrocannabinol and cannabidiol contamination of the seed may occur due to residual contamination of the outside of the seed coat, even under good agricultural/manufacturing practice. Rigorous cleaning methods, including washing, sieving and shelling, may help reduce or remove any cannabinoid contamination of seeds.

Reported gas chromatography (GC) analytical composition data of hemp seed oil (variety Fedora-19) from Leizer, *et al.*, (2000) includes significant portions of polyunsaturated fatty acids such as linoleic acid, oleic acid, stearic acid eichosanoic acids and palmitic acid, with more than 80% of the content being unsaturated fatty acids. Other trace compounds reported include Vitamin E (tocopherols), β -sitosterol, and terpenes (e.g. myrcene and caryophyllene) and salicylates.

Given this information, hemp seed oil products should not contain significant amounts of cannabinoids. The presence of cannabinoids in hemp seed oil is considered to arise from either a contamination or adulteration, rather than to be naturally occurring.

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.

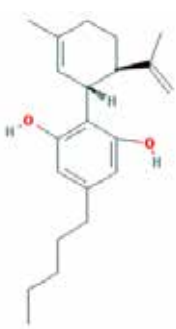
Information about the pharmacokinetics of the substance in humans is also accumulating. Oral absorption is slow and unpredictable relative to other routes of administration, possibly due to the chemical's poor water solubility. There is significant first pass metabolism where the concentration of ingested 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.

³⁹ [P1042 - Low THC Hemp Seeds as Food](#) and Leizer, C. *et al.*, [The Composition of Hemp Seed Oil and Its Potential as an Important Source of Nutrition \(pdf,145kb\)](#), J. Nutraceuticals, Functional & Medical Foods 2000 2(4) 35 - 53

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 1.5: Chemical information of cannabidiol

Property	Cannabidiol
CAS number	13956-29-1
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)
Chemical structure	
Molecular formula	C ₂₁ H ₃₀ O ₂
Molecular weight	314.5 g/mol

Tetrahydrocannabinol

THC is one of at least 113 cannabinoids identified in cannabis and is 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.

Pre-meeting public submissions

Eight (8) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. Two (2) of the submissions were in support of the proposed amendments to the Poisons Standard, one (1) in conditional support with amendments to the proposal, and two (2) that opposed the proposal. Three (3) of the submissions stated their opposition to the proposed amendments to the Poisons Standard but appeared to have misunderstood the applicant's proposal.

The main points provided in support of the amendment were:

- The proposed changes helpfully clarify the current industry confusion around cannabidiol scheduling. The changes do not alter the current public health risk and benefit calculation associated with medicinal cannabis or influence other matters raised in that section.
- The proposal would be a big step forward in legitimising medicinal cannabis as a viable medical treatment option for doctors and patients in Australia, especially considering the clinical justifications available for the use of cannabidiol-dominant products in a wide range of conditions.
- The wording in the current Schedule 4 entry for cannabidiol has meant that any preparation containing cannabidiol as an ingredient in less than 98% purity would be restricted to supply as a Schedule 8 medicine, regardless of the concentration of the ingredient in the product. The proposed change would broaden the scope of products that would fall into Schedule 4. If implemented, the proposed change will mean that cannabidiol dominant products containing other cannabinoids would fall into Schedule 4 as long as the concentration in the product of total cannabinoids other than cannabidiol does not exceed 1% w/v.
- From a scientific and clinical standpoint, this proposal is reasonable considering the favourable side-effect profiles of cannabidiol-dominant products, which justifies their designation as Schedule 4 medicines.
- The broadening of the scope of products that would fall into Schedule 4 will make access to medicinal cannabis products simpler for patients in need, owing to the less stringent state-based Schedule 4 requirements compared with the onerous Schedule 8 authorisations and dispensing protocols that doctors and pharmacists currently have to comply with for these products.
- Amendments suggested include:
 - *“CANNABIDIOL in preparations for therapeutic use where tetrahydrocannabinoids comprise no more than 1% w/v, and other cannabinoids found in cannabis comprise no more than 2% w/v”.*
 - § This suggested amendment will ensure that any given preparation will contain no more than 1% THC w/v, but may also contain other cannabinoids naturally present in the plant (as whole-plant extraction preparations will likely contain other cannabinoids in addition to THC).
 - *“CANNABIDIOL in preparations for therapeutic where other cannabinoids found in cannabis comprise no more than 2% w/v or w/w of the preparation and of these other cannabinoids, tetrahydrocannabinol comprises no more than 1 % w/v or w/w of the final preparation.”*
 - § The proposed limit in practice results in a much lower permitted actual THC content than 1.0% w/v or w/w. This is because all other cannabinoids present in the cannabidiol preparation must also be included in calculating the 1.0% limit. An alternative definition is proposed which allows for the presence of other cannabinoids, such that all cannabinoids (including THC) in total comprise up to 2.0% of the final preparation.
 - § The current proposed definition only refers to w/v, whereas - consistent with TGO93 - for certain products, a w/w calculation (as an alternative) would be more appropriate.

The main points provided in opposition of the amendment were:

- The proposed amendments referred by the delegate for consideration by the ACMS at the March 2018 meeting provided far more clarity than this latest proposal.
- Amendments suggested include:
 - ‘CANNABIDIOL in preparations for therapeutic use in which:
 - a) cannabidiol (together with any corresponding acid) comprises at least 98 per cent of the total cannabinoid content of the preparation; and
 - b) any cannabinoids present are only those naturally found in cannabis.’

Point a) with the proposed addition adequately addresses the levels of all other cannabinoids present in a cannabidiol preparation. It would assist clarity to explicitly state that tetrahydrocannabinol may be included in the ‘total cannabinoid content’ within the levels stipulated under the CANNABIDIOL entry and further, by cross referencing tetrahydrocannabinol to cannabidiol in the Index of the Poisons Standard.

In relation to point b) we suggest deleting ‘dealing with unavoidable impurities’.

- Slight modification of the 21 December 2017 wording released for consultation would be the preferred wording:
 - ‘CANNABIDIOL in preparations for therapeutic use in which:
 - a) cannabidiol comprises at least 98 per cent of the total cannabinoid content of the preparation; and
 - b) any cannabinoids present are only those naturally found in cannabis.’

Point a) adequately addresses the levels of all other cannabinoids present in a cannabidiol preparation. It would assist clarity to both explicitly state that tetrahydrocannabinol may be included in the ‘total cannabinoid content’ within the levels stipulated under the CANNABIDIOL entry and to cross reference tetrahydrocannabinol to cannabidiol in the Index of the Poisons Standard.

The main points provided in opposition but appear to have misunderstood the amendment were:

- The World Health Organisation has determined that CBD is safe and should not be scheduled under either of the two international treaties - the *Single Convention on Narcotic Drugs 1961* and the *Convention on Psychotropic Substances 1971*.⁴⁰
- CBD and THC are completely different substances and need to be regulated separate from one another. CBD does not require such strict regulation as it is non-toxic and non-addictive.⁴¹ Its safety has been demonstrated in multiple clinical studies.⁴²
- CBD is used globally to treat many conditions, most notably intractable epilepsy (Dravet's Syndrome). There are wider benefits in treating chronic pain and in palliative care for cancer patients.

⁴⁰ [World Health Organisation - Cannabidiol \(compound of cannabis\) Online Q&A](#)

⁴¹ Bergamaschi MM (2011). Safety and side effects of cannabidiol, a Cannabis Sativa constituent, Current Drug Safety, 6(4), 1-13.

⁴² Consroe P (1991) Controlled Clinical Trial of Cannabidiol in Huntington's Disease, Pharmacology Biochemistry and Behaviour, 40, 701-708.

- CBD is proving effective in combating the current abuse of opioids, where addiction and death are commonplace. In US jurisdictions where medicinal cannabis is available, prescriptions for opioids have fallen by as much as 25%.⁴³ This has negative implications for Australia as it is a major supplier to the opioid industry and derives some \$300 million per year from the sale of raw materials for drugs. Future export shortfalls can be more than covered by the Australian medicinal cannabis industry.
- In view of the acceptance that CBD is not a threat to health, lowering the accepted concentration levels is incongruous. The World Anti-Doping Agency (WADA) is one of the most stringent organisations in identifying substances that are either harmful or behaviour altering. In 2017, WADA removed CBD from the banned list whilst continuing to ban THC. This was in response to that fact that many athletes use CBD as an anti-inflammatory.⁴⁴
- Anecdotal evidence of efficacy of CBD.⁴⁵ CBD is used globally in treating numerous conditions, for example, Chemotherapy induced nausea and vomiting and epilepsy.^{46, 47, 48, 49}
- CBD oil is safe to use as a dietary supplement. The Australian New Zealand Food Standards recognises that CBD only has a therapeutic effect if taking more than 120 mg/day.

ACMS advice

The committee recommends that the current scheduling of cannabidiol remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice included:

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

- No additional information provided on risks and benefits of THC and other non-CBD cannabinoids to justify their down-scheduling.
- THC and selected other cannabinoids but not CBD are psychoactive.
- Cannabinoids may have benefits in a range of indications.

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

- There are a diverse range of formulations being developed containing a range of cannabinoid concentrations.

⁴³ [Science Daily - Legalized medical cannabis lowers opioid use, study finds](#)

⁴⁴ [Washington Post 2017 - While marijuana remains banned, WADA reverses course on hemp-derived compound CBD](#)

⁴⁵ [iPetitions - Make CBD \(Cannabidiol\) industrial hemp extract a non schedule substance for all Australians and legal to use and sell!](#)

⁴⁶ Geffrey AL (2015) Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy, *Epilepsia*, 56(8), 1246-1251.

⁴⁷ Devinsky O (2017) Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome, *The New England Journal of Medicine*, 376(21), 2011-2020.

⁴⁸ Devinsky O (2016) Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial, *The Lancet:Neurology*, 15(3), 270-278.

⁴⁹ Duran M (2010) Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting, *British Journal of Clinical Pharmacology*, 70(5), 1365-2125.

- The Schedule 4 entry for cannabidiol needs to define products for which the CBD is the predominant active compound and as such is likely to limit the ability to consume psychoactive THC doses from that product.

(e) the potential for abuse of a substance:

- Cannabis and its preparations and especially products containing THC are subject to abuse.

1.6 Paracetamol combined with ibuprofen

Delegate's interim decision

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

Reasons:

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

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

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

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

- A 10 day supply is sufficient to provide temporary relief of pain in alignment with the indications of the current two products being supplied. Should pain persist past this timeframe then review is appropriate.

(c) the toxicity of a substance:

- Risk of toxicity in case of overdose: A 50 tablet pack size would increase the total amount of paracetamol (10 g to 25 g) and ibuprofen (6 g to 10 g), depending on the S3 product pack size, which may result in significant toxicity (liver, gastrointestinal) in cases of an overdose.
- The toxicity is well-established. There is no new safety signals have arisen since this combination has been marketed (10 million patients' worldwide exposure; 1.5 million in New Zealand).

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

- There is a lack of clinical evidence to support the arguments to increase pack size.
- There appears to be no clinical need for a larger pack size for temporary relief of acute pain.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to paracetamol combined with ibuprofen;
- The advice received from the Advisory Committee on Medicines Scheduling (ACMS#24);
- 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; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for paracetamol combined with ibuprofen

Delegate's referral to ACMS

An application was submitted to amend the Poisons Standard with respect to paracetamol. The application proposed to amend the Schedule 3 and Schedule 4 entries for paracetamol.

Applicant's scheduling proposal and reasons

The applicant's proposed amendments to the [Poisons Standard](#) were:

Schedule 3 – Amend Entry

PARACETAMOL when combined with ibuprofen in a primary pack containing ~~30~~⁵⁰ dosage units or less **except** when included in Schedule 2.

Schedule 4 – Amend Entry

PARACETAMOL:

- a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than ~~30~~⁵⁰ dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;

- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection.

The applicant's reasons for the proposal were:

- Paracetamol and ibuprofen have been available for many years without a prescription in Australia. The safety of these over-the-counter (OTC) medicines is reflected in their classification, with small packs being unscheduled and larger packs (up to 100) in Schedule 2.
- Fixed dose combinations of paracetamol and ibuprofen offer greater analgesic efficacy at a lower dose while maintaining the acceptable safety profile of each active alone.
- A paracetamol 500 mg with ibuprofen 200 mg product was approved in Australia in July 2014. This combination of paracetamol with ibuprofen is a logical replacement for codeine/paracetamol and codeine/ibuprofen combinations as noted in the Scheduling Delegate's interim decision in relation to codeine on 1 October 2015:

"The combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the codeine-containing analgesics (CCAs), with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine".
- Currently in Australia, the maximum pack size of paracetamol with ibuprofen in Schedule 3 is 30 dose units and in Schedule 2 the maximum is 12 dose units.
- Given the up-scheduling of codeine-containing medicines to Schedule 4, the availability of larger pack sizes of ibuprofen/paracetamol combinations will allow pharmacists to exercise greater discretion in assisting clients with acute intermittent strong pain (e.g. migraine headache). This will mitigate pharmacists having to direct the customer to their doctor to obtain a prescription. The proposed amendment will allow pharmacists to offer a safer, more economical and convenient alternative to the stronger analgesics available through medical practitioners.
- The proposed amendment will facilitate the management of acute intermittent strong pain in the pharmacy setting with safe and effective OTC medicines. This will have a positive impact on public health, whereby minimising the impact on the health system and improving access and affordability of OTC pain relief for strong pain.
- Pharmacists will be in a position to reinforce label warnings present on all OTC analgesics, including not to take the medicine for more than 3 days at a time.
- Consumers can treat their acute pain (with pharmacist advice) with one tablet of the paracetamol 500 mg with ibuprofen 200 mg product and consume less than half of the active ingredients than the same ingredients used alone. This '*active-sparing*' is in line with the Quality Use of Medicines (QUM) principles in Australia's National Medicines Policy.
- The total amount of paracetamol and ibuprofen in the proposed 50 pack is less than half the amounts present in the existing Schedule 2 packs of the separate ingredients.

Current scheduling status

Paracetamol

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

Schedule 4

PARACETAMOL:

- a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules **except** in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules **except** when included in Schedule 2;
- h) for injection.

Schedule 3

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

Schedule 2

PARACETAMOL for therapeutic use:

- a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

- e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- f) in other preparations **except**:
 - i) when included in Schedule 3 or 4; or
 - ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,
 - (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (C) not labelled for the treatment of children 6 years of age or less, and
 - (D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin; or
 - iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) packed in blister or strip packaging or in a container with a child-resistant closure,
 - (B) in a primary pack containing not more than 20 tablets or capsules,
 - (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (D) not labelled for the treatment of children 6 years of age or less, and
 - (E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin.

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

Appendix F, Part 3

PARACETAMOL

Warning Statements: 97 (Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor) AND/OR 98 (Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor), 99 (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage), 100 (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist).

Ibuprofen

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

Schedule 4

IBUPROFEN **except**:

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

Schedule 3

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

- a) with a recommended daily dose of 1200 mg or less of ibuprofen; and
- b) not for the treatment of children under 12 years of age;

except when included in or expressly excluded from Schedule 2.

Schedule 2

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

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or
- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
 - i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);
 - ii) packed in blister or strip packaging or in a container with a child-resistant closure;
 - iii) in a primary pack containing not more than 25 dosage units;
 - iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;
 - v) not labelled for the treatment of children 6 years of age or less; and
 - vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

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

Appendix F, Part 3

IBUPROFEN

Warning Statements:

101: Don't use [*this product/name of the product*]:

If you have a stomach ulcer.

In the last 3 months of pregnancy. [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.]

If you are allergic to (name of substance) or anti-inflammatory medicines

104: Unless a doctor has told you to, don't use [*this product/name of the product*]:

For more than a few days at a time.

With other medicines containing (name of substance) or other anti-inflammatory medicines.

If you have asthma.

If you are pregnant. [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.*]

Scheduling history

Paracetamol/ibuprofen combinations

In June 2010, the National Drugs and Poisons Scheduling Committee (NDPSC) considered the scheduling of a combination of ibuprofen and paracetamol and agreed that the current scheduling remained appropriate – Schedule 2 for combinations of up to 200 mg ibuprofen and 500 mg paracetamol in packs of up to 100 dosage units.

In February 2011, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal from the Advisory Committee on Non-Prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination. The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice and in September 2011, the Poisons Standard was amended to move paracetamol combined with ibuprofen to Schedule 3 in pack sizes of 30 units or less and Schedule 4 (all other products).

In October 2012, the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

In March 2015 the ACMS considered a proposal to create a new entry for paracetamol/ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remains appropriate. The ACMS considered that the public health risk from advertising is that it would be seen as first line therapy and that there was little evidence to support the applicant claim that an Appendix H entry would transfer demand from codeine combination analgesics to non-codeine combination analgesics. The delegate agreed with the committee's advice.

In November 2015 the ACMS considered a proposal to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS supported the proposal on the basis of the well-established safety profile, low risk of diversion/abuse/addiction and that the medicine provides an effective option for short term use for moderate pain. Following an interim decision in alignment with committee advice and subsequent consideration of the submissions on the interim decision, the delegate decided to vary the interim decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considered it is more appropriate to limit the Schedule 2 entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive. The implementation date was 1 June 2016.

In July 2017, the ACMS considered a proposal to amend the Schedule 2 entry of ibuprofen combined with paracetamol to increase the pack size from 12 to 24 dosage units or less. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remains appropriate. The ACMS considered the risk of overdosing on ibuprofen combined with paracetamol, the risk of potential adverse effects if the Schedule 2 pack size increase, the reduction in pharmacist advice and the potential for increased delay in consumers seeking advice. The delegate agreed to the committee's advice and the scheduling remained unchanged.

Australian regulatory history

Ibuprofen combined with paracetamol

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has 21 products that contain ibuprofen combined with paracetamol.

In the last 30 years there have been 3 reported cases of adverse events related to ibuprofen combined with paracetamol in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 3 cases with a single suspected medicine and no cases where death was the reported outcome.

Paracetamol

The ARTG has 776 products that contain paracetamol.

In the last 30 years there have been 3400 reported cases of adverse events related to paracetamol in the DAEN: 1337 cases with a single suspected medicine and 148 cases where death was the reported outcome.

According to the [TGA Ingredient Database](#), paracetamol is:

- Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

Ibuprofen

The ARTG has 217 products that contain ibuprofen.

In the last 30 years there have been 1335 reported cases of adverse events related to ibuprofen in the DAEN: 889 cases with a single suspected medicine and 42 cases where death was the reported outcome.

According to the [TGA Ingredient Database](#), ibuprofen is:

- Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
- Not available as an Equivalent Ingredient in any application.

International regulations

The paracetamol 500 mg with ibuprofen 200 mg product has been approved as an over-the-counter medicine in many countries including the United Kingdom, Poland, New Zealand, Ukraine, Russia, Saudi Arabia, United Arab Emirates, Kuwait, Bahrain, Oman, Qatar and Yemen. It is Pharmacy Only in the United Kingdom and Poland and it is a 'general sale' medicine in New Zealand in pack sizes up to 20 dose units and 'pharmacy medicine' in pack sizes of up to 100 dose units. In the United Kingdom, the paracetamol 500 mg with ibuprofen 200 mg product is available as a 'pharmacy' medicine in packs of up to 32 tablets.

Paracetamol 500 mg with ibuprofen 150 mg tablets were approved in New Zealand in March 2009.

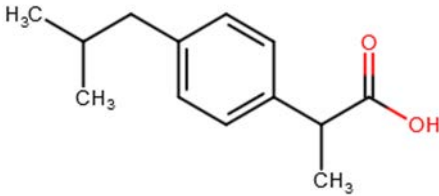
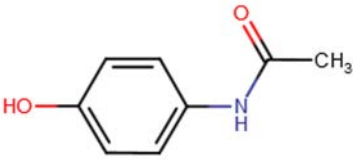
Substance summary

Paracetamol is a *p*-aminophenol derivative that has analgesic and antipyretic effects and has weak anti-inflammatory activity. It has been available in Australia since the 1970s and is marketed in many OTC medicine brands. Like ibuprofen it is indicated for the management of mild to moderate pain in conditions such as period pain, headache, muscular pain, dental pain, cold and flu symptoms, back pain, rheumatic pain and sinus pain and to reduce fever.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an OTC medicine in the management of mild to moderate pain and inflammation in conditions such as period pain, headache, muscular pain, dental pain, cold and flu symptoms, back pain, arthritic pain and sinus pain. It is also used to reduce fever.

Table 1.6: Chemical information for ibuprofen and paracetamol

Property	Ibuprofen	Paracetamol
CAS name	15687-27-1	103-90-2
IUPAC and/or common and/or other names	(<i>RS</i>)-2-(4-(2-Methylpropyl)phenyl)propanoic acid (IUPAC); α -Methyl-4-(isobutyl)phenylacetic acid, (\pm)-2-(4-Isobutylphenyl)propanoic acid;	<i>N</i> -(4-hydroxyphenyl)acetamide (IUPAC); 4'-Hydroxyacetanilide; 4-Acetamidophenol, <i>N</i> -Acetyl-4-aminophenol; <i>N</i> -acetyl- <i>p</i> -aminophenol

Property	Ibuprofen	Paracetamol
	isobutylphenylpropionic acid.	(APAP); Acetaminophen.
Chemical structure		
Molecular formula	C ₁₃ H ₁₈ O ₂	C ₈ H ₉ NO ₂
Molecular weight	206.3 g/mol	151.2 g/mol

Pre-meeting public submissions

Five (5) public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. Three (3) submissions supported and two (2) opposed the proposed amendments.

The main points provided in support of the amendment were:

- The proposal will better reflect the current scheduling principles and would align Australian with NZ scheduling of the combination products.
- The NZ classification of the combination paracetamol and ibuprofen products is the same as the classification of the individual substances. In NZ, the combination products are Pharmacy Medicines in pack sizes of 21 to 100 tablets/capsules and are available for general sale in pack sizes of up to 20 tablets/capsules.
- Individually, paracetamol and ibuprofen have a long history of use in Australia and a well-documented, favourable safety profile. The low risks associated with these ingredients are reflected in their unscheduled availability in small pack sizes. Paracetamol and ibuprofen combination products offer greater analgesic efficacy at a lower dose while maintaining the acceptable safety profile of each substance used separately.
- The total amount of paracetamol and ibuprofen present in the proposed 50 pack in Schedule 3 will be less than half the amounts present in the existing Schedule 2 packs of the individual ingredients. Consumers using the combination products as directed on the product label will take less than half the maximum recommended dose of paracetamol and ibuprofen used separately. This 'active-sparing' effect is in line with the Quality Use of Medicines principles in Australia's National Medicines Policy.
- The current Australian ibuprofen and paracetamol combination products are a logical replacement for the low dose codeine-paracetamol and codeine-ibuprofen combinations that were up-scheduled to Schedule 4 on 1 February 2018.

- The scheduling cut-off should be based on the number of dosage units as opposed to a scheduling cut-off based on a number of days' supply for the following reasons:
 - All the other Schedule entries for divided preparations of paracetamol and ibuprofen are based on maximum pack sizes and maximum quantities of active ingredient per tablet or capsule (thereby ensuring consistency of the maximum amount of active per pack). The same approach should be taken with this proposal to provide consistency with the Schedule entries; and
 - The quantities of paracetamol and ibuprofen, as well as the dosing instructions for the two major combination products, are different. A 3 day supply of The paracetamol 500 mg with ibuprofen 200 mg product is a maximum of 9 tablets and a 3 day supply of the paracetamol 500 mg with ibuprofen 150 mg product is a maximum of 24 tablets. To ensure that products in the same Schedule contain similar total quantities of active ingredients, and to avoid confusion in the marketplace, the scheduling of the combination should be based on pack size.
- The labelling of these products contains appropriate warning statements to facilitate appropriate use as per the TGA Medicines Advisory Statement Specifications (MASS 2017). Pharmacists are also available at the point of supply to provide advice and referral if needed.
- The proposal will allow pharmacists to exercise greater discretion in managing clients with acute intermittent strong pain (e.g. from migraine headache). It will also reduce the pressure on general practitioners resulting from demand for larger packs of stronger analgesics from patients with a legitimate need for treatment of acute intermittent strong pain.

The main points provided in opposition of the amendment were:

- There is no need for an increase in pack size as combination paracetamol and ibuprofen products are indicated for the temporary relief of mild to moderate acute pain. Allowing access to larger quantities is not appropriate. If pain persists, consumers should be seeking medical advice from a healthcare professional. The provision of a smaller pack size will prompt patients to seek advice from a pharmacist if continued supply of these medicines is required, thus better managing their pain.
- Paracetamol and ibuprofen combination products should not be used long term without consultation with a health professional.
- Liver damage is possible in adults who have taken 10 g (equivalent of 20 tablets) of paracetamol. There is no need for paracetamol and ibuprofen combination products, or any other analgesic product indicated for the use of short term pain, to be available in larger quantities than necessary.
- The availability to larger quantities of any analgesic increases the likelihood of misadventure. As a general principle, consumers should only have access to clinically appropriate quantities.
- Paracetamol and ibuprofen combination products have not been on the market for long and caution should be taken in increasing the pack size from 30 to 50.
- Easy access to paracetamol and ibuprofen, either in combination or as individual ingredients, poses a risk to the public. All analgesics should be available from retailers where professional advice is available.

- A TGA conducted review of NSAIDs demonstrated that prolonged use is associated with cardiovascular risks and hepatotoxicity.⁵⁰
- With the up-scheduling of codeine-containing medicines, there may be an increase in consumers previously using codeine-containing medicines inappropriately for chronic pain seeking an alternative. This may highlight some unknown risks. However, there would appear to be little potential for abuse of these particular products. It is these consumers that would benefit from consultation with a health care professional rather than access to a larger quantity of a medicine that may be inappropriate for their condition.

ACMS advice

The committee recommends that the current scheduling of paracetamol remains appropriate.

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

The reasons for the advice included:

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

- The risk of increasing pack size would be potentially delaying consumers seeking further advice from a health practitioner.
- Risks: Proposed pack size may encourage treatment of chronic pain. Treatment of chronic pain condition which is outside the approved indication (acute short term pain) for this combination, resulting in delayed treatment that could result in long term morbidity. Current 30 pack size allows for about 3 x 3 days treatment if the acute pain is intermittent (eg. migraine headache, tension headache). Risk of toxicity in case of overdose.

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

- No different to pack size of 30 tablets.

(c) the toxicity of a substance:

- The toxicity is well-established. There is no new safety signals have arisen since this combination has been marketed (10 million patients worldwide exposure; 1.5 million in New Zealand).

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

- As for the pack size of 30 tablets.

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

- Lack of clinical evidence to support the arguments to increase pack size.

⁵⁰ Australian Government. (2015). [Submissions and TGA response: Non-steroidal anti-inflammatory drugs \(diclofenac, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid and naproxen\): proposed additional advisory statement for medicines](#). Therapeutic Goods Administration; and Australian Government. (2016) [Nonsteroidal anti-inflammatory drugs \(NSAIDs\) and spontaneous abortion](#). Therapeutic Goods Administration.

2. Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #19)

2.1 2-Butoxyethanol

Delegate's 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 2-butoxyethanol as follows:

Schedule 6 – Amend Entry

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

- a) in plant growth regulator preparations containing 20 percent or less of such substances; or
- b) in other preparations containing 10 percent or less of such substances.

Proposed implementation date: 1 February 2019

Reasons:

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

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

– Benefits:

§ 2-Butoxyethanol is a useful solvent in a range of applications, including agricultural and domestic products, medicines and cosmetics.

– Risks:

§ The most sensitive toxicological end point is the destruction of red blood cells (haemolysis). Additional toxicities include neurotoxicity (loss of coordination, sluggishness and narcosis) and nephrotoxicity.

§ 2-butoxyethanol has low to moderate acute toxicity via oral, dermal and inhalation routes, and severe skin and eye irritancy.

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

– 2-Butoxyethanol is used as a solvent in a range of applications.

– 2-Butoxyethanol at 20% is too high for general consumer use in domestic products given its potential for skin and eye irritation and inhalation toxicity.

(c) the toxicity of a substance:

– 2-butoxyethanol has adverse effects on the CNS (e.g. loss of coordination, sluggishness and narcosis).

– 2-Butoxyethanol has haemolytic effects. Studies suggest that rats are more susceptible

to haemolytic effects than humans and that rats exposed to 2-butoxyethanol develop tolerance and show reduced haemolytic effects over time, or on future exposure.

- 2-Butoxyethanol is readily absorbed via all routes of exposure (inhalation, dermal, ingestion) with low to moderate acute toxicity via oral, dermal and inhalation routes.
- 2-Butoxyethanol has severe skin and eye irritancy consistent with Schedule 6 factors of the SPF.
- Respiratory irritant consistent with Schedule 6 factors of the SPF.
- In-vitro studies show no mutagenicity or genotoxicity.

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

- Toxicity of 2-butoxyethanol is mitigated when formulated as a plant grown regulator, allowing a higher percentage cut off.
- Although the inhalation and skin and eye irritation data of a 20% 2-butoxyethanol preparation aligns with the Schedule 5 SPF factors, mandatory GHS labelling of plant growth regulator preparations as regulated by the APVMA should be sufficient.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to 2-butoxyethanol;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #19);
- 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for 2-butoxyethanol

Delegate's referral to ACCS/ACMS

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to 2-butoxyethanol. The application proposes to amend the Schedule 6 entry for 2-butoxyethanol in the Poisons Standard to increase the exemption concentration from 10 per cent to 20 per cent.

Applicant's scheduling proposal and reasons

The application proposed the following amendments to the Poisons Standard:

Schedule 6 – Amend Entry

2-BUTOXYETHANOL and its ACETATES **except** in preparations containing ~~10~~**20** per cent or less of such substances.

The applicant's reasons for the proposal were:

- The APVMA recently evaluated acute toxicity data for a product containing approximately 20% 2-butoxyethanol (final concentration was 175 g/L). The formulated product had low toxicity via the oral, dermal and inhalation routes of exposure as follows:
 - Oral LD₅₀ in rats was 3129 mg/kg;
 - Dermal LD₅₀ in rats was >5000 mg/kg; and
 - Inhalation LC₅₀ in rats was >2120 mg/m³ (nose-only; maximum attainable concentration).
- The primary eye irritation study with the formulated product revealed slight irritation that resolved completely by 48 hours following administration of the test material.
- The primary skin irritation study with the formulated product revealed slight irritation that resolved completely by 72 hours following administration of the test material.
- The first aid instructions in the Poisons Standard (Appendix E, Standard Statements A, E2 and S1) for 2-butoxyethanol are inconsistent with the eye and skin irritation.

Current scheduling status

2-Butoxyethanol is in Schedule 6, Appendix E and Appendix F of the Poisons Standard as follows:

Schedule 6

2-BUTOXYETHANOL and its ACETATES **except** in preparations containing 10 per cent or less of such substances.

Appendix E, Part 2

2-BUTOXYETHANOL and its acetates

General 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)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3

2-BUTOXYETHANOL and its acetates

Safety Directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

Scheduling history

August 1995 meeting of the National Drugs and Poisons Schedule Committee (NDPSC)

In August 1995, the NDPSC considered a proposal to either exempt 2-butoxyethanol from scheduling or create a separate entry for 2-butoxyethanol in Schedule 5. At this time, 2-butoxyethanol was captured by the generic entry in Schedule 6 for ethylene glycol monoalkyl ethers and their acetates except those containing 10% or less. The committee considered that the acute toxicological profile, particularly in regard to eye and skin irritancy and the ready absorption by the dermal route, indicated that Schedule 6 remained appropriate for this compound and did not support the proposal for rescheduling.

August 1998 meeting of the National Drugs and Poisons Schedule Committee (NDPSC)

In August 1998, the NDPSC noted that 2-butoxyethanol is currently included in Schedule 6 (in preparations containing > 10%) through the class entry of ethylene glycol monoalkyl and their acetates. However, the committee agreed to create a new separate entry in Schedule 6 for 2-butoxyethanol and its acetates with an exception for preparations containing 10 per cent or less. It was agreed that Schedule 6 was appropriate due to the formulation, handling and use of cleaning products containing 2-butoxyethanol which may give rise to a risk of adverse health effects and that 2-butoxyethanol is considered acutely more toxic than most glycol ethers. The Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates was also amended at this time to add the exception 'when separately specified in these Schedules'.

November 2014 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #12)

In November 2014, the ACCS considered a [proposal to create separate entries for a number of ethylene glycol monoalkyl ethers and their acetates, including 2-butoxyethanol](#). The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme had reviewed a number of chemicals in this class and recommended that separate entries be created for selected chemicals (see [Human health tier II assessment for Ethanol, 2-butoxy acetate](#)). The advice from the ACCS was that the toxicity profile of 2-butoxyethanol is consistent with Schedule 6 criteria and that it was adequately captured by the current generic entry for ethylene glycol monoalkyl ethers and their acetates, and the specific 2-butoxyethanol and its acetates Schedule 6 entry. Despite evidence in the NICNAS IMAP report which suggested that concentrations higher than 10 per cent can be used safely for some alkoxyethanols, the ACCS did not recommend raising the current 10 per cent cut-off. The delegate accepted the ACCS advice that the current scheduling of 2-butoxyethanol remained appropriate.

Scheduling history of ethylene glycol monoalkyl ethers and their acetates

In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered the scheduling of ethylene glycol monoalkyl ethers and their acetates. The PSC noted that ethylene glycol monomethyl- and monoethyl ethers were the most toxic of the series, which demonstrated significant testicular effects, reproductive toxicity, haematological effects and were toxic at inhalation levels at the threshold limit value (TLV). The PSC also noted that other alkyl ethers demonstrated haematological effects which increased with chain lengths. The PSC therefore decided to include preparations containing 5 per cent or more ethylene glycol monoalkyl ethers and their acetates in Schedule 6.

In February 1985, the PSC reconsidered the November 1984 decision and decided to raise the Schedule 6 ethylene glycol monoalkyl ethers and their acetates exemption cut-off from 5 per cent to 10 per cent.

In November 2013, based on the ACCS advice, the delegate created a separate schedule entry for hexyloxyethanol with a cut-off level to exempt from scheduling for preparations containing 10 per cent of less of hexyloxyethanol. The delegate also decided to create new Appendices E, F and I entries specifically for hexyloxyethanol. The delegate's decision was based on the fact that hexyloxyethanol's toxicity profile was different from the chemical class ethylene glycol monoalkyl ethers.

Australian regulations

2-Butoxyethanol is listed on the Australian Inventory of Chemical Substances (AICS). An assessment of its uses in cleaning products was completed in 1996. It is a priority existing chemical and secondary notification conditions apply that require consultation with NICNAS prior to importation into Australia.

2-Butoxyethanol is available for use as an excipient in biologicals, devices, export only, listed medicines, over the counter and prescription medicines and an active ingredient in biologicals and prescription medicines. Restrictions apply to its use in listed medicines according to the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#):

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirement(s) applying to the ingredient in Column 2
968	BUTOXYETHANOL	E	Only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye. The concentration in the medicine must be no more than 0.1%.

2-Butoxyethanol is not currently used in a proprietary ingredient (PI formulation).

Butoxyethanol is an excipient ingredient in 5 products on the [Australian Register of Therapeutic Goods \(ARTG\)](#). Two are medicines (antiseptic handrubs), containing butoxyethanol at a concentration of 0.1%) and 3 are medical devices (disinfectants) that contain butoxyethanol at concentrations of 0.25-9 % w/w.

International regulations

Canada

Canada completed its assessment of 2-butoxyethanol in 2002 and as a result developed regulations to limit its concentration in a variety of consumer products intended for indoor use: [2-Butoxyethanol Regulations \(SOR/2006-347\)](#).

United States

2-Butoxyethanol appears in the Appendix A to section [1926.55-1970 American Conference of Governmental Industrial Hygienist's threshold limit values of airborne contaminants](#) of the Electronic Code of Federal Regulations as follows:

Substance	CAS No.	ppm	mg/m ³	Skin Designation
2-Butoxyethanol	111-76-2	50	240	X

Butoxyethanol is in Annex III to Regulation (EC) No 1223/2009 and is permitted for use as a solvent in oxidative hair dye products at 4% and in non-oxidative hair dye products at 2%. Butoxyethanol is not permitted for use in aerosol dispenser (sprays).

Substance summary

2-Butoxyethanol is very widely used in industrial, trade and domestic cleaning applications. Common formulations which include 2-butoxyethanol are surface cleaners, floor strippers, paints, laundry detergents, rust removers, oven and carpet cleaners. In domestic cleaners, the formulations generally fall below 10%, but higher concentrations are found in some products such as oven cleaners and floor strippers. Some industrial cleaners contain greater than 90% 2-butoxyethanol. 2-Butoxyethanol is also used in medicines and medical devices currently registered on the ARTG.

The source of the below information on the toxicological profile for 2-butoxyethanol is from the [Concise International Chemical Assessment \(CICAD\), Document 10](#).

Table 2.1A: Chemical information for 2-butoxyethanol

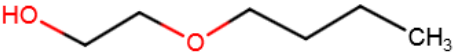
Property	2-Butoxyethanol
CAS number	111-76-2
IUPAC and/or common and/or other names	Ethylene glycol mono- <i>n</i> -butyl ether; butyl cellosolve; 2-butoxy-1-ethanol; 2- <i>n</i> -butoxyethanol; butyl glycol; butyl monoether glycol
Chemical structure	
Molecular formula	C ₆ H ₁₄ O ₂
Molecular weight	118.2 g/mol

Table 2.1B: Acute toxicity end-points for 2-butoxyethanol

Toxicity	Species	2-butoxyethanol	SPF (2018) Classification
Acute oral toxicity LD ₅₀ (mg/kg)	Rat	2500 mg/kg	5
	Mouse	1400 mg/kg	6
	Guinea pig	1200 mg/kg	6
	Rabbit	320 mg/kg	6

Toxicity	Species	2-butoxyethanol	SPF (2018) Classification
Acute dermal toxicity LD ₅₀ (mg/kg)	Guinea pig	2000 mg/kg	5/6
	Rabbit	404-502 mg/kg	6
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat (male, 4h)	2347 mg/m ³	6
	Rat (female, 4h)	2174 mg/m ³	6
	Mouse (7h)	3381 mg/m ³	5
	Guinea pig (1h)	3140 mg/m ³	5
Skin irritation	Rabbit	Severe irritant	6
Eye irritation	Rabbit	Severe irritant	6
Skin sensitisation	Guinea pig	Non-sensitiser	-

Acute toxicity

2-Butoxyethanol is moderately toxic via the oral and dermal routes of exposure and it is of low toxicity via the inhalation route of exposure.

Skin irritation

When tested undiluted, 2-butoxyethanol is a severe skin irritant.

Eye irritation

When tested undiluted, 2-butoxyethanol is a severe eye irritant (CICAD 1998). A study conducted in 1989 tested a series of 2-butoxyethanol concentrations (10, 20, 30, 70 and 100%) for eye irritation. The results showed that 100% was severely irritating, at 30 and 70%, 2-butoxyethanol was moderately irritating, and at 10 and 20%, 2-butoxyethanol was reported in the study as mildly irritating. However, the Draize scores indicate that at those concentrations, it is practically non-irritating (scores of 1/110 and 2/110 at 10% and 20%, respectively) (Kennah *et al.*, 1989).

Sensitization

2-butoxyethanol is not considered to be a skin sensitiser.

Repeat-dose toxicity

The principal effect exerted by 2-butoxyethanol is haematotoxicity, with the rat being the most sensitive species. The results of *in vitro* studies indicate that human red blood cells are not as sensitive as rat red blood cells to the haemolytic effects of 2-butoxyethanol and 2-butoxyacetic acid and also that red blood cells are more sensitive to haemolysis by 2-butoxyacetic acid than to

haemolysis by 2-butoxyethanol. In rats, adverse effects on the central nervous system, kidneys, and liver occur at higher exposure concentrations than do haemolytic effects.

Genotoxicity

2-Butoxyethanol is not considered to be genotoxic.

Carcinogenicity

2-Butoxyethanol is not classified with respect to carcinogenicity. No studies are available.

Reproduction and developmental toxicity

In animals, adverse effects on reproduction and fetal development have not been observed below maternally toxic doses.

Observation in humans

Based on limited data from case reports and one laboratory study, similar acute effects, including haemolytic and CNS effects are observed in humans and rats exposed to 2-butoxyethanol, although the effects are observed at much higher exposure concentrations in humans than in rats.

Pre-meeting public submissions

No public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations.

Joint ACMS-ACCS advice

The committee recommended that the Schedule 6 entry for 2-butoxyethanol in the Poisons Standard be amended as follows:

Schedule 6 – Amend Entry

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

- a) **in plant growth regulator preparations containing 20 percent or less of such substances; or**
- b) **in other** preparations containing 10 percent or less of such substances.

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

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

The reasons for the advice included:

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

- Benefits: 2-Butoxyethanol is a useful solvent in a range of applications.
- Risk: 2-Butoxyethanol has haemolytic and Central Nervous System (CNS) effects, low to moderate acute toxicity via oral, dermal and inhalation routes, and severe skin and eye irritancy.

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

- 2-Butoxyethanol is used as a solvent in a range of applications.

(c) the toxicity of a substance:

- 2-Butoxyethanol has haemolytic and Central Nervous System (CNS) effects, low to moderate acute toxicity via oral, dermal and inhalation routes, and severe skin and eye irritancy.
- Exposed test subjects (rats) developed tolerance to 2-butoxyethanol (haemolytic effects).
- Skin and eye irritation consistent with Schedule 6.
- Respiratory irritant consistent with Schedule 6.

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

- Toxicity of 2-butoxyethanol is mitigated when formulated as a plant grown regulator, allowing a higher percentage cut off.

2.2 Dimethyl sulfoxide (DMSO)

Delegate's 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 dimethyl sulfoxide as follows:

Schedule 6 – Amend Entry

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

- a) when not for therapeutic use; or
- b) in cosmetic preparations; or
- c) for the treatment of animals:
 - i) when combined with no other therapeutic substance(s);
 - ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or
 - iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide; or
- d) in other preparations **except** when containing 10 per cent or less of dimethyl sulfoxide.

Schedule 4 – Amend Entry

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

- a) when included in Schedule 6; or
- b) in in vitro test kits; or
- c) **when used as a flavour component when the total flavour content is 5 per cent or less of the preparation.**

Proposed implementation date: 1 February 2019

Reasons:

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

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

- Risks:
 - § DMSO is a carrier/universal solvent that enhances skin penetration of other substances and thus renders internal organs permeable to drugs and chemicals, leading to enhanced therapeutic and/or toxic responses.
 - § DMSO is an eye and skin irritant in undiluted form.
- Benefits:
 - § DMSO has a number of therapeutic uses due to its low toxicity.

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

- DMSO is used as a commercial solvent.
- DMSO is found in a number of human therapeutic preparations, including for dermal use, at concentrations greater than 10%.
- Only non-therapeutic uses of DMSO are covered by the proposed exemption.
- DMSO is prohibited in cosmetic products in the EU (Regulation (EC) No 1223/2009 – Annex II).

(c) the toxicity of a substance:

- DMSO is of low acute toxicity but is considered both a skin and eye irritant at concentrated doses. It is a mild irritant to both skin and eyes.
- Toxicity of dilute DMSO preparations is low (at most, slight skin and eye irritation only).
- DMSO enhanced dermal penetration of other compounds and may thereby enhance toxicity of these compounds.
- DMSO is not expected to be genotoxic, carcinogenic, nor to have reproductive or developmental toxicity.
- Long-term oral or dermal administration produces only slight toxicity. The proposed exposure to DMSO is not a health concern.

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

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

(e) the potential for abuse of a substance:

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

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

- The intention of the Schedule 4 amendment is to align this entry with the requirements of the *Therapeutic Goods (Permissible Ingredients) Determination No. 2 of 2018*.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to dimethyl sulfoxide;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #19);
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for dimethyl sulfoxide

Delegate's referral to ACCS/ACMS

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to dimethyl sulfoxide (DMSO). The application proposed to amend the Schedule 6 entry for in the Poisons Standard by introducing a new exemption concentration cut-off.

Applicant's scheduling proposal and reasons

The application proposed the following amendments to the Poisons Standard:

Schedule 6 – Amend Entry

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

- a) when in preparations not for therapeutic use **and containing 10 per cent or less of dimethyl sulfoxide**; or
- b) for the treatment of animals:
 - i) when combined with no other therapeutic substance(s);
 - ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or
 - iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide.

The applicant's reasons for the proposal were:

- DMSO was found to have low acute oral, dermal and inhalational toxicity. DMSO is a non-skin sensitiser but is a slight skin and eye irritant at high concentrations. Repeat dose toxicity studies performed by oral, dermal, and inhalational routes revealed no toxicity at a limit dose (1000 mg/kg/day). DMSO is also non-carcinogenic, non-genotoxic and has a low potential for any reproductive or developmental toxicity.
- The potential for slight acute skin and eye irritation appears to be concentration dependent but only at levels in excess of 66%, primarily due to the heat generated when DMSO comes into contact with water (a potent exothermic reaction).
- At low concentrations (approximately 10% and less), DMSO is not expected to induce skin or eye irritation in humans.
- DMSO is currently in use in a number of human therapeutic preparations, including dermal topical formulations, at concentrations greater than 10%.

Current scheduling status

DMSO is listed in Schedules 4 and 6, and Appendices E and F of the Poisons Standard as follows:

Schedule 4

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

- a) when included in Schedule 6; or
- b) in in vitro test kits.

Schedule 6

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

- a) when not for therapeutic use; or
- b) for the treatment of animals:
 - i) when combined with no other therapeutic substance(s);
 - ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or
 - iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide.

Appendix E, Part 2

DIMETHYL SULFOXIDE

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

Appendix F, Part 3

DIMETHYL SULFOXIDE	Warning Statement	Safety Direction
a) when not packed and labelled for therapeutic use.	27 (Not for therapeutic use)	1 (Avoid contact with eyes), 4 (Avoid contact with skin), 5 (Wear protective gloves when mixing or using), 8 (Avoid breathing dust (or) vapour (or) spray mist)
b) when packed and labelled for the treatment of animals.	49 (WARNING – Do not mix with other medication except on veterinarian's advice)	1 (Avoid contact with eyes), 4 (Avoid contact with skin), 5 (Wear protective gloves when mixing or using), 8 (Avoid breathing dust (or) vapour (or) spray mist)

Index

DIMETHYL SULFOXIDE

cross reference: COPPER SALICYLATE, METHYL SALICYLATE

Schedule 6

Schedule 4

Appendix E, Part 2

Appendix F, Part 3

Scheduling history

DMSO has a long and thorough scheduling history dating back to 1965, whereby all uses have been considered. DMSO was first listed in Schedule 6 (Poison) of the Poisons Standard in 1965 based on toxicological concerns including potentially causing eye lens opacities. This entry included the warning statement in the label 'avoid contact with the skin and avoid breathing its vapour'. It was subsequently listed in Schedule 4 (Prescription Only Medicine) for therapeutic use based on concerns to regulate high-dose human therapeutic use (including clinical trials) for a variety of arthritic conditions. However, DMSO was only to be used with approval of the Commonwealth Director-General of Health.

During the 1980s – 1990s, the Schedule 6 entry was amended to enable some dermally applied veterinary products to escape Schedule 4 controls. The principal concern of DMSO and the reasons for scheduling was to alert those applying the medications to the known propensity for DMSO to markedly enhance the skin penetration of other substances and its capacity to render other organs permeable to drugs and chemicals. This could lead to an enhanced therapeutic response via more extensive absorption of any active therapeutic substances in the preparations. Due to this property, any DMSO-containing formulation should be treated as a new drug. It was also for this reason that the Schedule 6 amendments specified that it only applies when there no other therapeutically active substance in the formulation, or it is a specific formulation that has been assessed as suitable for a Schedule 6 listing. There were also reports of DMSO being abused or prescribed illegally. The Schedule 6 listing also provides for an Appendix F Warning Statement relating to the potential for enhanced skin absorption of other active substances.

Australian regulations

DMSO is permitted for use as an excipient in biologicals, devices, listed medicines and prescription medicines; and as an active ingredient in biologicals and prescription medicines. Restrictions apply to its use in listed medicines according to the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#) as follows:

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirement(s) applying to the ingredient in Column 2
1829	DIMETHYL SULFOXIDE	E	Permitted for use only in combination with other permitted ingredients as a flavour. If used in a flavour the total flavour concentration in a medicine must be no more than 5%.

There are 33 products (31 biologicals and 2 medical devices) on the Australian Register of Therapeutic Goods (ARTG) that contain DMSO at concentrations up to 27%.

DMSO (methane, sulfinylbis-) is listed on the Australian Inventory of Chemical Substances (AICS) and a [Human Health Tier II Assessment for Methane, sulfinylbis-](#) has been completed by NICNAS.

Agricultural and veterinary chemicals containing DMSO are listed on the APVMA's [PubCRIS](#). Currently, DMSO is present in some agricultural chemicals at concentrations of up to 515 g/L, and in veterinary chemical preparations of up to 900 mg/g.

International regulations

European Union

DMSO has been considered by the European Chemicals Agency (ECHA) as part of the [REACH program](#).

One orphan designation has been granted by the European Commission for DMSO for the treatment of severe closed traumatic brain injury.

United States (US)

DMSO is a prescription medicine in the US and can be used in concentrations up to 50% in medicines for human use. In animals, DMSO is approved for use only in horses and dogs.

Canada

There are 9 prescription medicines that contain DMSO as an active ingredient in Canada, only 3 of which (1 human medicine and 2 veterinary medicines) are currently marketed. Concentrations of DMSO used in the medicines range from 50% (human medicines) to 90% (veterinary medicines).

Substance summary

Table 2.2A: Chemical information for dimethyl sulfoxide

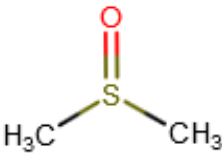
Property	Dimethyl sulfoxide
CAS number	67-68-5
IUPAC and/or common and/or other names	Dimethyl sulfoxide (IUPAC); sulfinylbismethane (CAS)
Chemical structure	
Molecular formula	C ₂ H ₆ OS
Molecular weight	78.1 g/mol

Table 2.2B: Acute toxicity end-points for dimethyl sulfoxide

Toxicity	Species	Dimethyl sulfoxide	SPF (2018) Classification
Acute oral toxicity LD ₅₀ (mg/kg)	Rat	28300 mg/kg	-
Acute dermal toxicity LD ₅₀ (mg/kg)	Rat	40000 mg/kg	-
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat (4h)	>5330 mg/m ³	-
Skin irritation	Rabbit	Slight skin irritant when applied undiluted	6
Eye irritation	Rabbit	Slight eye irritant when instilled undiluted	6
Skin sensitisation	Mouse (LLNA)	Non-sensitiser	-

Acute toxicity

DMSO has low acute oral, dermal and inhalational toxicity.

Skin irritation

When applied undiluted (>66%), DMSO is a skin irritant.

When applied in diluted form (<66%), DMSO is a slight skin irritant.

Dermal exposure to DMSO causes skin reactions, erythema and pruritus, which are seen immediately after contact with the undiluted substance. Solutions of 70% are generally well tolerated in humans without symptoms. The skin reaction to the undiluted substance is considered to be the result of the exothermic reaction (heat releasing) process of DMSO when mixed with water. DMSO, being very hygroscopic readily draws water from the atmosphere (and surrounding dermal or ocular tissues).

In a controlled study, 1 g of gel containing 80% DMSO was applied to the skin of 78 human subjects daily for 2 weeks. In addition to the skin reactions noted above, sedation developed in 52%, headaches in 42%, sleepiness in 18% and nausea in 32% of subjects. Moreover, there were no changes noted in the eyes of the subjects.

Eye irritation

When instilled undiluted (>66%), DMSO is an eye irritant.

When instilled in diluted form (<66%), DMSO is a slight eye irritant.

Sensitisation

DMSO is not considered to be a skin sensitiser.

Repeat-dose toxicity

The main effects of very high doses of DMSO administered to experimental animals by intravenous injection are morphological and functional changes in the liver and kidney. Long-term oral or dermal administration produces only slight toxicity. Hepatotoxicity and nephrotoxicity have not been described in humans (MAK, 1992).

Genotoxicity

DMSO is not considered to be genotoxic.

Carcinogenicity

Based on the limited data available, DMSO is not expected to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, DMSO is not considered to have reproductive or developmental toxicity.

Observation in humans

Observations in humans after repeated dermal exposure indicate that DMSO can cause skin dryness or cracking due to its defatting (dissolving dermal lipids) and drying characteristics. Exposure to undiluted (>66%) preparations of DMSO are associated with eye and skin irritation. There are no other critical health effects expected from exposure to diluted preparations of the chemical.

Pre-meeting public submissions

No public submissions were received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations.

Joint ACMS-ACCS advice

The committee recommended that the current Schedule 6 entry for dimethyl sulfoxide be amended as follows:

Schedule 6 – Amend Entry

DIMETHYL SULFOXIDE (excluding dimethyl sulfone):

- a) in cosmetic preparations; or
- b) for the treatment of animals:
 - i) when combined with no other therapeutic substance(s);
 - ii) in liquid preparations containing copper salicylate and 1 per cent or less of methyl salicylate as the only other therapeutic substances; or
 - iii) in clay poultices containing 2 per cent or less of dimethyl sulfoxide; or
- c) in other preparations **except** when containing 10 per cent or less of dimethyl sulfoxide.

The committee also recommended that the current Schedule 4 entry for dimethyl sulfoxide be amended to align this entry with the requirements of the *Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018*, which specifies that in listed medicines, dimethyl sulfoxide is permitted for use only in combination with other permitted ingredients as a flavour and if used in a flavour, the total flavour concentration in a medicine must be no more than 5%. The amendments suggested for the Schedule 4 dimethyl sulfoxide entry are as follows:

Schedule 4 – Current Entry

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

- a) when included in Schedule 6; or
- b) in in vitro test kits; or
- c) when used as a flavour component when the total flavour content is 5 per cent or less of the preparation.

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

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

The reasons for the advice included:

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

- Combinations of DMSO with other toxic substances account for most of DMSO's toxic potential.
- DMSO is an eye and skin irritant in undiluted form.
- DMSO has a number of therapeutic uses due to its low toxicity.

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

- DMSO is used for both therapeutic purposes and as a commercial solvent.
- Only non-therapeutic uses of DMSO are covered by the proposed exemption.

(c) the toxicity of a substance:

- DMSO is of low acute toxicity but is considered both a skin and eye irritant at concentrated doses. It is a mild irritant to both skin and eyes.
- Toxicity of dilute DMSO preparations is low (at most, slight skin and eye irritation only).
- DMSO enhances dermal penetration of other compounds and may thereby enhance toxicity of these compounds.

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

- Schedule 6 products require labelling and packaging in accordance with the Poisons Standard. Labelling of unscheduled products is the responsibility of the manufacturer / supplier.

(e) the potential for abuse of a substance:

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

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

- The intention of the committee advice regarding amendments to the Schedule 4 entry is to align this entry with the requirements of the *Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018*.

2.3 Aliphatic allyl esters

Delegate's 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 aliphatic allyl esters as follows:

Schedule 7 – Amend Entry

ALLYL ALCOHOL **except**

- a) in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl ester; or
- b) when separately specified in these Schedules.

Schedule 6 – New Entry

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

Proposed implementation date: 1 February 2019

Reasons:

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

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

- Allyl esters are widely used without significant adverse events.
- Benefits: Allyl esters are used as an excipient in biologicals, and medicines.
- Risks: Potential for the toxic metabolites (allyl alcohol and acrolein) to be formed following oral exposure to allyl esters.

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

- Allyl esters are generally used as flavours or fragrances in cosmetics, therapeutic goods, household products and commercial products.
- Aliphatic allyl esters are used in therapeutic products, including listed medicines at concentrations at or below 5%.
- 5% cut-off consistent with the Therapeutic Goods (Permissible Ingredients) Determination No.2 of 2018 listing of these substances.

(c) the toxicity of a substance:

- Based on the toxicological data (specifically acute oral and dermal toxicity), allyl esters have a lower acute toxicity profile than allyl alcohols.
- Allyl esters have an acute oral and dermal toxicity profile consistent with Schedule 6 [Scheduling Policy Framework](#) (SPF) criteria:

- § Moderate to high oral and dermal toxicity.
- § Low to moderate acute toxicity via inhalational exposure.
- § Allyl acetate is corrosive.
- § Allyl cyclohexanepropionate is a moderate skin sensitiser in guinea pigs.
- § Potential for the toxic metabolites (allyl alcohol and acrolein) to be formed following oral exposure to allyl esters;
 - Allyl alcohol is reported to have very high acute oral, dermal and inhalation toxicity.

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

- Align with international regulations for cosmetic products where aliphatic allyl esters are used in fragrance ingredients, provided that the free allyl alcohol is less than 0.1% in the ester

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The application to amend the current Poisons Standard with respect to aliphatic allyl esters;
- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #19);
- the public submission 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for aliphatic allyl esters

Delegate's referral to ACCS/ACMS

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) program to amend the Poisons Standard with respect to aliphatic allyl esters. The application proposed to amend the Schedule 7 entry for allyl alcohol and create a new Schedule 6 entry for allyl esters.

Applicant's scheduling proposal and reasons

The application proposed the following amendments to the Poisons Standard:

1. Amend the current Schedule 7 entry for allyl alcohol to exclude allyl esters as its derivatives, and to allow low levels of allyl alcohol as an impurity in preparations containing allyl esters at 5 per cent or less as follows:

Schedule 7 – Amend Entry

ALLYL ALCOHOL (including its derivatives) **except**

- a) when included in Schedule 6; and
- b) in preparations containing 5 per cent or less of allyl esters and containing less than 0.1 per cent allyl alcohol by weight of allyl esters.

2. Create a new Schedule 6 entry for allyl esters for use in consumer products, with a purity criterion and a concentration cut-off at 5 per cent, below which the requirements of the standard do not apply as follows:

Schedule 6 – New Entry

ALLYL ESTERS containing less than 0.1 per cent allyl alcohol by weight of allyl ester **except** in preparations containing 5 per cent or less of allyl esters and containing less than 0.1 per cent allyl alcohol by weight of allyl esters.

The applicant's reasons for the proposal were:

- Aliphatic allyl esters have international restrictions on their use in cosmetic products – the level of free allyl alcohol in preparations is restricted to be less than 0.1 %, based on the delayed irritant potential of allyl alcohol;
- As derivatives, allyl esters fall within the scope of the Schedule 7 entry for allyl alcohol;
- Aliphatic allyl esters are reported to be used as fragrance ingredients in cosmetic and domestic products overseas at concentrations ≤5 %, and are therefore likely to be used in similar products in Australia at ≤5 %; and
- Acute toxicity values for aliphatic allyl esters are consistent with inclusion in Schedule 6.

Current scheduling status

Aliphatic allyl esters are not specifically scheduled in the Poisons Standard but are captured by the Schedule 7 and Appendix J entries for allyl alcohol as derivatives, as follows:

Schedule 7

ALLYL ALCOHOL.

Appendix J, Part 2

ALLYL ALCOHOL

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

Scheduling history

Aliphatic allyl esters are not currently specifically scheduled and have not been previously considered for scheduling. Therefore a scheduling history is not available.

Scheduling of allyl alcohol

Allyl alcohol was placed in Schedule 7 between 1972 and 1980. In February 1989, the Drugs and Poisons Schedule Committee (DPSC) considered the toxicology of allyl alcohol as part of the review of Schedule 7 substances. The committee noted the toxicological profile of allyl alcohol as a severely toxic substance with an LD₅₀ (oral, rat) of 64 mg/kg, LD₅₀ (oral mice) 85 mg/kg, and LC₅₀ (inhalation rat) of 391 mg/m³. Allyl alcohol was assessed as a severe dermal irritant in rabbits as well as a severe eye irritant sometimes leading to opacity. In sub-chronic studies in rats, rabbits, guinea pigs and dogs the liver and kidneys were seen as the target organs, but the effects seen were considered mild and reversible. Furthermore, allyl alcohol was considered to be mutagenic. In view of the severe acute toxic potential in humans, the good penetration by all routes of exposure and the lack of animal data, the committee recommended that allyl alcohol should remain in Schedule 7. Appendix J would be reviewed (no agricultural uses permitted) following information from industry if allyl alcohol has an industrial use.

In November 1989, the DPSC noted that no reply had been received from industry regarding industrial uses of allyl alcohol. Nevertheless, the committee decided that the Appendix J entry for allyl alcohol should be amended to include restrictions 3 (Should be available to authorised or licensed persons), 5 (Should be available for approved research purposes) and 7 (Should be available for industrial and manufacturing purposes).

Australian regulations

Aliphatic allyl esters CAS 1797-74-6, 2835-39-4, 4728-82-9, 68132-80-9 and 7493-72-3 are not included in the Therapeutic Goods (Permissible Ingredients) Determination No.2 of 2018 and do not appear to be included in any products on the [Australian Register of Therapeutic Goods \(ARTG\)](#).

Aliphatic allyl ester CAS 2705-87-5 (under the name 'ALLYL CYCLOHEXANEPROPIONATE') is included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#) as follows:

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
441	ALLYL CYCLOHEXANEPROPIONATE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Allyl cyclohexanepropionate is permitted for use as an excipient in biologicals, listed medicine and prescription medicines; and as an active ingredient in biologicals and prescription medicines.

Allyl cyclohexanepropionate is in 158 products (Medicine and Other Therapeutic Good) on the [ARTG](#).

Allyl cyclohexanepropionate is used in 10 proprietary ingredient (PI) formulations.

Aliphatic allyl ester CAS 123-68-2 (under the name 'ALLYL HEXANOATE') is included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#) as follows:

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
445	ALLYL HEXANOATE	E	<p>Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.</p> <p>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.</p> <p>If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.</p>

Allyl hexanoate is permitted for use as an excipient in biologicals, devices, listed medicine and prescription medicines; and as an active ingredient in biologicals and prescription medicines.

Allyl hexanoate is in 420 products (Medicine and Other Therapeutic Good) on the [ARTG](#).

Allyl hexanoate is used in 10 PI formulations.

Aliphatic allyl ester CAS 142-19-8 (under the names 'ALLYL HEPTANOATE' and 'ALLYL HEPTYLATE') is included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#) as follows:

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
443	ALLYL HEPTANOATE	E	<p>Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.</p> <p>If used in a flavour the total flavour concentration in a medicine must be no more than 5%.</p> <p>If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.</p>

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
444	ALLYL HEPTYLATE	E	Permitted for use only in combination with other permitted ingredients as a flavour. If used in a flavour the total flavour concentration in a medicine must be no more than 5%.

Allyl heptanoate is permitted for use as an excipient in biologicals, devices, listed and prescription medicines, and as an active ingredient in biologicals and prescription medicines. Allyl heptylate is permitted for use as an excipient in listed medicines.

Allyl heptanoate is in 100 products (Medicine and Other Therapeutic Good) on the [ARTG](#); and allyl heptylate is not in any products on the [ARTG](#).

Allyl heptanoate is used in 10 PI formulations; and allyl heptylate is used in 2 PI formulations.

Aliphatic allyl ester CAS 4230-97-1 (under the name 'ALLYL CAPRYLATE') is included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#) as follows:

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
440	ALLYL CAPRYLATE	E	Permitted for use only in combination with other permitted ingredients as a flavour. If used in a flavour the total flavour concentration in a medicine must be no more than 5%.

Allyl caprylate is permitted for use as an excipient in biologicals, devices, listed medicine and prescription medicines; and as an active ingredient in biologicals and prescription medicines.

Allyl caprylate is not in any products on the Australian Register of Therapeutic Goods (ARTG).

Allyl caprylate is used in 2 PI formulations.

International regulations

Aliphatic allyl esters are listed on the following:

- European Union Cosmetics Regulation 1223/2009 Annex III – List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down (the level of free allyl alcohol in the ester shall be less than 0.1 %); and
- New Zealand Cosmetic Products Group Standard – Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

- Allyl esters are specified as 'should only be used when the level of free allyl alcohol in the ester is less than 0.1 %. This recommendation is based on the delayed irritant potential of allyl alcohol' (IFRA, 2017).

Substance summary

Table 2.3A: Chemical information of aliphatic allyl esters

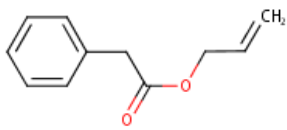
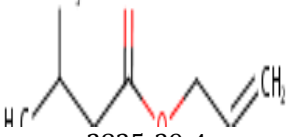
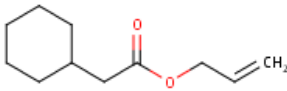
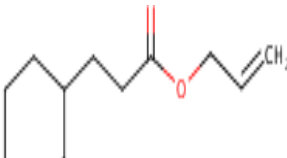
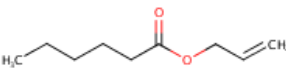
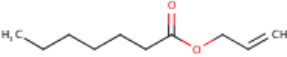
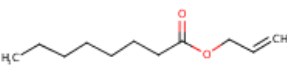
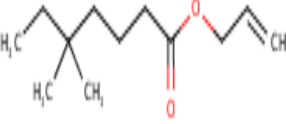
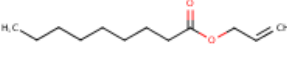
 <p>1797-74-6 allyl phenylacetate; benzeneacetic acid, 2-propenyl ester (CAS); 2-propenyl benzeneacetate</p>	 <p>2835-39-4 allyl isovalerate; butanoic acid, 3- methyl-, 2-propenyl ester (CAS); 2-propenyl isovalerate</p>	 <p>4728-82-9 allyl cyclohexaneacetate; cyclohexaneacetic acid, 2- propenyl ester (CAS); acetic acid, cyclohexyl-, allyl ester</p>
 <p>2705-87-5 allyl cyclohexanepropionate; cyclohexanepropanoic acid, 2- propenyl ester (CAS)</p>	 <p>123-68-2 allyl hexanoate; hexanoic acid, 2- propenyl ester (CAS); allyl caproate</p>	 <p>142-19-8 allyl heptanoate; heptanoic acid, 2-propenyl ester (CAS)</p>
 <p>4230-97-1 allyl octanoate; octanoic acid, 2- propenyl ester (CAS); allyl caprylate</p>	 <p>68132-80-9 allyl trimethylhexanoate; hexanoic acid, trimethyl-, 2- propenyl ester (CAS)</p>	 <p>7493-72-3 allyl nonanoate; nonanoic acid, 2- propenyl ester (CAS)</p>

Table 2.3B: Acute toxicity end-points for allyl esters

Toxicity	Species	Allyl Esters	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg)	Rat	218–1400 mg/kg (for suitable analogues)	Schedule 6
	Mouse	≥500 mg/kg (for suitable analogues)	
	Guinea pig	280–444 mg/kg (for suitable analogues)	
Acute dermal toxicity LD ₅₀ (mg/kg)	Rabbit	300–1600 mg/kg (for suitable analogues)	Schedule 6
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	N/A	No data available.	N/A
Skin irritation	Rabbit	Suitable analogue chemicals slightly to moderately irritating to the skin when applied undiluted.	Schedule 5
	Human	Skin irritation in humans assessed by patch testing.	
Eye irritation	Rabbit	Slightly irritating (allyl hexanoate and allyl cyclohexanepropionate).	Schedule 5
Skin sensitisation (Guinea pig maximisation test and human case reports)	Guinea pig	Not sensitising (allyl heptanoate) and moderately sensitising (allyl cyclohexanepropionate).	Schedule 5
	Human	Suitable analogue chemicals were not skin sensitisers.	

Table 2.3C: Acute toxicity end-points for allyl alcohol

Toxicity	Species	Allyl Esters	SPF (2018) Classification
Acute oral toxicity LD ₅₀ (mg/kg)	Rat	64–105 mg/kg	Schedule 6
	Mouse	85–96 mg/kg	
	Rabbit	52–72 mg/kg	
Acute dermal toxicity LD ₅₀ (mg/kg)	Rabbit	45 and 89 mg/kg	Schedule 7
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	>240 mg/m ³ and >530 mg/m ³	Schedule 7
Skin irritation	Rabbit	Slightly irritating to the skin when applied undiluted.	Schedule 7 (human)
	Human	Intensely irritating to the skin.	
Eye irritation	Rabbit	Irritating undiluted.	Schedule 7
	Human	Irritating at 5 ppm (11.9 mg/m ³) as vapour and corneal necrosis and temporary blindness at 25 ppm (59.4 mg/m ³).	
Skin sensitisation (Guinea pig maximisation test and human case reports)	Guinea pig	Not sensitising.	N/A
	Human		

Acute toxicity

Allyl esters

Allyl esters are considered to have moderate to high acute oral and dermal toxicity in animals. No data are available for acute inhalation toxicity.

- **Oral** – The reported oral median lethal dose (LD₅₀) values were:
 - allyl hexanoate, 218–393 mg/kg in rats and 280 mg/kg in guinea pigs;
 - allyl heptanoate, 500 mg/kg in rats, 630 mg/kg in mice, and 444 mg/kg in guinea pigs
 - allyl isovalerate, 230 mg/kg in rats and ≥500 mg/kg in mice;
 - allyl phenylacetate, 650 mg/kg in rats;
 - allyl cyclohexanepropionate, 585 mg/kg in rats and 380 mg/kg in guinea pigs;
 - allyl cyclohexaneacetate, 900 mg/kg in rats; and
 - allyl trimethylhexanoate, 1400 mg/kg in rats.
- **Dermal** – The reported dermal LD₅₀ values in rabbits are:
 - allyl hexanoate, 300 mg/kg;
 - allyl heptanoate, 810 mg/kg;
 - allyl isovalerate, 560 mg/kg;
 - allyl cyclohexanepropionate, 1600 mg/kg; and
 - allyl cyclohexaneacetate, 1250 mg/kg.

Allyl alcohol

Allyl alcohol is reported to have very high acute oral, dermal and inhalation toxicity in animals. The chemical is extremely toxic to humans.

- **Oral** – The chemical has very high acute toxicity in rats, mice and in rabbits. Additionally, the chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic if swallowed’ (H301) in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia) aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The available data support this classification.
- **Dermal** – The chemical has very high acute toxicity in rabbits with reported dermal LD₅₀ values at 45 and 89 mg/kg. The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic in contact with skin’ (H311) in the HCIS (Safe Work Australia). The available data support an amendment to this classification to ‘Acute Toxicity Category 2’ and hazard statement ‘Fatal in contact with skin’ (H310) which was recommended in the NICNAS IMAP report.
- **Inhalation** – The reported median lethal concentration (LC₅₀) values in rats for 4-hour exposures to the mist or vapour of the chemical are >240 mg/m³ and >530 mg/m³. The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic if inhaled’ (H331) in the HCIS (Safe Work Australia). The available

data support an amendment to this classification to 'Acute Toxicity Category 2' and hazard statement 'Fatal if inhaled' (H330).

- **Observation in Humans** – In a case report, a 55-year old man who ingested the chemical (estimated maximum dose of 212 g) died within 100 minutes.

Irritation

Allyl esters

- **Skin** – Allyl isovalerate, allyl hexanoate, allyl heptanoate, allyl phenylacetate and allyl cyclohexaneacetate have been reported as slightly to moderately irritating to rabbit skin. However, data available are not sufficient for hazard classification. The skin irritation potential of allyl cyclohexanepropionate was assessed using the Human Skin Model Test (OECD TG 439) and was not considered to be a potential skin irritant.
- **Eye** – Allyl hexanoate and allyl cyclohexanepropionate are slight eye irritants. However, the incidence and severity of these effects are not sufficient to warrant hazard classification.
- **Observation in Humans** – In a 48-hour patch test, allyl hexanoate was applied on the forearms of human volunteers (n = 5). Four subjects displayed grade 1 irritation. However in a subsequent study by the same author using both allyl hexanoate and heptanoate, no signs of irritation were observed in 5 volunteers. Allyl isovalerate was not irritating when applied to the backs of 28 subjects in a closed patch test. Allyl cyclohexaneacetate produced slight irritation at a concentration of 4 % in petrolatum in a 48-hour closed-patch test on human subjects.

Allyl cyclohexanepropionate was not an irritant in a patch test on 129 human volunteers at concentrations up to 2 %. The chemical (0.3 mL) was applied (occlusively) to the back of the volunteers for 24 hours and responses were assessed up to 5 days following exposure. The chemical caused less irritation compared with the other allyl esters tested (allyl hexanoate, allyl cyclohexyloxyacetate, allyl phenoxyacetate). In another 24-hour patch test, allyl cyclohexanepropionate (20 µg) was positive in 8 out of 10 volunteers, and allyl heptanoate was positive in 9 out of 10 volunteers. The concentrations were not reported. Although these chemicals were reported to be acute irritants, the data were not considered to be relevant for classification.

Allyl phenylacetate showed mixed results in two 48-hour closed patch tests on human subjects, when tested up to 12 % in petrolatum. No irritation reactions were reported initially, but were observed when retested. When tested at 6 %, it was a significant irritant in a majority of human subjects.

Allyl alcohol

- **Skin** – Allyl alcohol is slightly irritating to the skin of rabbits when applied undiluted. The chemical is classified as hazardous with hazard category 'Skin irritation – category 2' and hazard statement 'Causes skin irritation' (H315) in the Safe Work Australia. The available data in humans (see Observation in Humans) support this classification.
- **Eye** – Allyl alcohol was irritating to the eyes of male rabbits when applied undiluted for 4 hours. The mean scores at 24, 48 and 72 hours for erythema, chemosis, and corneal opacity were 2.89, 1.23 and 2.09, respectively. Additionally, the chemical is classified as hazardous with hazard category 'Eye irritation – Category 2' and hazard statement 'Causes serious eye irritation' (H319) in the HCIS (Safe Work Australia). The available data in animals (conjunctival and corneal damage) and in humans (see Observation in Humans) support this classification.

- **Observation in humans** – Reported toxicity effects for allyl alcohol vapour include eye discomfort at 5 ppm, and corneal necrosis and temporary blindness at 25 ppm. Exposure to air that is moderately contaminated with the chemical (concentration not stated) causes excessive secretion of tears, pain behind the eyes, sensitivity to light and blurring of vision. Despite effects persisting for several hours, neither increased sensitivity nor tolerance developed for the above effects. The vapour and liquid of the chemical is reported to be intensely irritating to the skin and mucous membranes.

Contact with the liquid causes delayed-onset skin irritation and burns. Additionally, skin absorption leads to deep pain which may be due to muscle spasm.

Sensitisation

Allyl esters

The chemicals overall are not expected to have skin sensitisation potential. However, allyl cyclohexanecarboxylate was reported as a moderate skin sensitizer in guinea pigs.

Limited human data have shown that the chemicals are not skin sensitizers in human volunteers.

Allyl alcohol

Allyl alcohol is not expected to have skin sensitisation potential based on data in a guinea pig maximisation study. No allergic responses were reported in humans.

Repeat-dose toxicity

Allyl esters

The effects observed in the repeated dose studies suggest that the liver, stomach and hematopoietic system in rats and mice are the primary sites affected following treatment with allyl esters. The mechanism of hepatotoxicity of allyl esters is linked to its rapid hydrolysis in the liver to the metabolites allyl alcohol and acrolein. Many studies on allyl alcohol and acrolein have showed liver damage, often localised to the periportal region. Short chain allyl esters which are not fragrance ingredients (e.g. allyl acetate) have reported effects at doses above 12 mg/kg/day in rats. Other longer chain allyl esters in the group have effect levels above 84 mg/kg/day. No data are available for repeated dermal and repeated inhalation exposure.

Allyl alcohol

Allyl alcohol is considered to cause serious damage to health from repeated oral exposure. The effects observed in the repeat dose oral studies indicate that the liver and forestomach in rats and mice are the primary target sites, with mice being less sensitive to toxicity than rats. Forestomach effects may be due to primary irritation. Hepatotoxicity was evident at ≥ 25 mg/kg/day in rats and is stated to be due to biotransformation to acrolein. A sex difference in hepatotoxicity in rats was reported to be correlated with the greater alcohol dehydrogenase activity in female rats than in male rats. In a sub-chronic toxicity study, the no observed adverse effect level (NOAEL) in rats was 3 mg/kg based on histopathological effects seen at 6 mg/kg/day. The NOAEL in mice was 6 mg/kg/day based on forestomach squamous epithelial hyperplasia seen at 12 mg/kg/day.

Genotoxicity

Allyl esters and allyl alcohol are not considered to be genotoxic.

Carcinogenicity

Allyl esters

Results from a two-year carcinogenicity study suggested that allyl isovalerate caused increased incidence of haematopoietic system neoplasms (mononuclear cell leukaemia in male rats and malignant lymphomas in female mice). However, in the absence of more comprehensive information and based on the results for allyl alcohol, allyl esters cannot be considered possible human carcinogens.

Allyl alcohol

Based on the available data for the chemical and its metabolite acrolein, the chemical does not have carcinogenic potential.

Reproduction and developmental toxicity

Based on the data available, allyl esters and allyl alcohol are not likely to be reproductive or developmental toxicants.

Public exposure

Two of these chemicals (CAS Nos. 123-68-2 and 2705-87-5) have reported domestic uses in Australia. The chemicals in this group are also reported to be used in cosmetics and domestic products, particularly perfumery, overseas. The general public could be exposed through the skin when using cosmetic and domestic products containing the chemicals.

At present, as derivatives, the chemicals fall within the scope of the listing of 'ALLYL ALCOHOL' in Schedule 7 of the SUSMP, and it is probable that perfumery imported from the EU or elsewhere is not compliant with this scheduling entry. Therefore, it is recommended that allyl esters are exempted from the Schedule 7 entry, considering the acute toxicity values are consistent with inclusion in Schedule 6. A concentration cut-off (5 %) for allyl esters is recommended. At this concentration, the product LD₅₀ based on allyl ester content would be close to or greater than 5000 mg/kg. This proposed cut-off is also consistent with the maximum concentration reported in fragrance products (not intended for direct human contact, such as air fresheners) as stated in the NICNAS IMAP report. In addition, to maintain alignment with EU restrictions, it is also recommended that a concentration cut-off for allyl alcohol in allyl esters be included.

This requires consequential changes to scheduling of allyl alcohol to exclude the derivatives, allyl esters, meeting a purity criterion consistent with the EU.

While creation of a general exception for allyl esters could impact on the shorter chain allyl esters which have greater local effects, they do not have any reported cosmetic or domestic uses.

Pre-meeting public submissions

One (1) public submission was received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. The submission supported the proposal with amendments.

The main points in provided in conditional support of the amendment were:

- Support for the exclusion of the 9 aliphatic allyl esters listed from the Schedule 7 entry for allyl alcohol to allow the use of these globally available fragrance ingredients in domestic and consumer products in Australia. Support for aligning the regulatory treatment of these substances with that already in place in comparable overseas economies.

- The 9 aliphatic allyl esters are currently listed in Annex III of the EU Cosmetics Regulation 'List of substances which cosmetic products must not contain except subject to the restrictions laid down' with a specific condition on the permissible level of free allyl alcohol: 'Level of free allyl alcohol in the ester should be less than 0.1%'. The proposed Poisons Standard schedule exemption for aliphatic allyl esters in the allyl alcohol entry should refer to the level of free allyl alcohol (the term 'free' is not currently included in the proposal as drafted).
- There are no restrictions on the concentration of the esters (provided the level of free allyl alcohol is less than 0.1%) that may be used in cosmetic products marketed in the EU (and other countries which follow the EU Cosmetics Regulation such as the ASEAN countries and New Zealand which are geographically close trading partners). The proposed amendment as currently worded may result in the inadvertent regulation of substances other than those that have been listed above i.e. that have been identified to be of concern in the IMAP assessment. We would therefore urge consideration of an approach that scheduled only these 9 substances that have been identified as being of concern i.e. listing by CAS number.

The public submission will be made available on the TGA website at [Public submissions on scheduling matters](#).

Joint ACMS-ACCS advice

The committee recommended that the current Schedule 7 entry for allyl alcohol be amended as follows:

Schedule 7 – Amend Entry

ALLYL ALCOHOL **except**

- a) in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl ester; or
- b) when separately specified in these Schedules.

The committee also recommended that a new Schedule 6 entry for allyl esters be created as follows:

Schedule 6 – New Entry

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

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

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

The reasons for the advice included

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

- Allyl esters are widely used without significant adverse events.
- Benefits: Allyl esters are used as an excipient in biologicals, and medicines.
- Risks: Potential for toxic metabolites to be formed.

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

- Allyl esters are generally used as flavours or fragrances in cosmetics, therapeutic goods, household products and commercial products.

(c) the toxicity of a substance:

- Acute oral and dermal toxicity consistent with a schedule 6 listing.
 - § 5% cut-off consistent with the Therapeutic Goods (Permissible Ingredients) Determination No. 2 of 2018 listings of these substances.
 - § Moderate to high oral and dermal toxicity.
 - § Low to moderate acute toxicity via inhalational exposure.
 - § Allyl acetate is corrosive.
 - § Allyl cyclohexanepropionate is a moderate skin sensitiser in guinea pigs.
 - § Toxic metabolites formed: Allyl alcohol and acrolein.

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

- Align with international regulations where free allyl alcohol is less than 0.1% in the ester.

2.4 Astodrimmer sodium

Delegate's 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 astodrimmer sodium as follows:

Schedule 3 – New Entry

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

Appendix F, Part 1 – New Entries

109	See your healthcare provider if you consider that you may be at risk of a Sexually Transmitted Infection (STI).
110	See your healthcare provider if your symptoms persist or recur, or your condition worsens, as these symptoms may be indicative another infection, including a Sexually Transmitted Infection (STI).
111	See your healthcare provider if you are pregnant or plan to become pregnant, or you are breastfeeding or plan to breastfeed; you should seek advice of your healthcare provider before using this product.

Appendix F, Part 3 – New Entry

ASTODRIMER SODIUM

Warning statements: 63 (See a doctor if you are pregnant or diabetic), 64 (See a doctor if not better after 7 days), 69 (If symptoms recur within two weeks of completing the course, consult a doctor), 75 (Do not use for more than 7 days unless a doctor has told you to), 109, 110, 111.

Appendix H – New Entry

ASTODRIMER SODIUM for the treatment and relief of bacterial vaginosis (BV)

Proposed date of effect of the proposed amendment: 1 February 2019

Reasons for the interim decision:

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

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

– Risks:

§ The risks associated with astodrimmer remaining unscheduled include the potential for self-treatment without health professional involvement to exclude sexually transmitted infections (STIs). Although the consumer can identify the symptoms that may be treated by the medicine, counselling and verification by a pharmacist is required before use. In addition, with astodrimmer in Schedule 3 and pharmacist

involvement in their care, women are more likely to seek further advice from a doctor should over-the-counter (OTC) treatment be ineffective.

– Benefits:

§ The current need for a woman with BV to be treated with the involvement of a doctor is because there are currently no non-antibiotic treatments. Astodrimmer is a non-antibiotic option for the treatment of BV, which is an imbalance in the normal vaginal flora and not an infection caused by a specific pathogen. It is usually a non-serious condition.

§ The use of astodrimmer to treat BV could avoid several serious pregnancy risks associated with BV including chorio-amnionitis, spontaneous abortion, preterm delivery, low birth weight, postpartum and post-abortion endometritis.

§ There are minimal adverse effects associated with use of the substance

On balance, the benefits of using the substance with a pharmacist but not a doctor's intervention outweigh the risks of it remaining unscheduled.

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

- Bacterial vaginosis is a very common condition in women, with prevalence estimates of 10-50%. Treatment of the symptoms of such a medical condition requires health professional assessment. Consultation with a pharmacist is considered to be warranted to exclude the possibility of misdiagnosis.
- The proposed scheduling is consistent with the current availability of vaginal antifungal preparations.

(c) the toxicity of a substance:

- Astodrimmer is of low toxicity, with minimal risk of systemic toxicity or local irritant/inflammatory effects. These characteristics are appropriate for an OTC product.

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

- A number of mandatory label statements have been proposed including the requirement for an accurate description of BV in the product packaging and instructions for use. These labelling requirements will contribute to the appropriate use of the substance and provide advice on the course of action for consumers if treatment is unsuccessful or if symptoms recur.

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

- An Appendix H entry is proposed. Advertising of astodrimmer is appropriate in alignment with currently available vaginal fungal treatments. There is likely to be an improvement in public awareness of BV if astodrimmer is made available OTC under Schedule 3 and in Appendix H.
- The product has only been recently launched worldwide so there is no post-marketing surveillance data available as yet and S3 provides a greater opportunity to manage risks of usage.
- Astodrimmer may be suitable for Schedule 2 in the future; however further experience is required on consumer diagnostic accuracy and missed diagnosis of STIs.

Delegate's considerations

The delegate considered the following in regards to this interim decision:

- The advice received from the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #19);
- the public submission 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; and (f) any other matters that the Secretary considers necessary to protect public health.

Scheduling proposal

The pre-meeting scheduling proposal was published on the TGA website on 12 April 2018 at [Consultation: Proposed amendments to the Poisons Standard being referred to the June 2018 meetings of the ACCS, ACMS and Joint ACCS/ACMS](#).

Background information for astodrimmer sodium

Delegate's referral to ACCS/ACMS

A delegate of the Secretary of the Department of Health proposed an amendment to the Poisons Standard by creating a new Schedule 4 entry for astodrimmer sodium.

Applicant's scheduling proposal and reasons

The proposed amendments to the Poisons Standard that were referred to the Joint ACMS-ACCS #19 for advice are reflected below:

Schedule 4 – New Entry

ASTODRIMER SODIUM except when used as a condom lubricant.

The reasons for the proposal were:

- Astodrimmer sodium is a topical microbicide that is used in a class 2A medical device for the treatment of bacterial vaginosis (BV), and for prevention of sexually transmitted diseases as a condom lubricant.
- BV requires medical diagnosis, management and monitoring before astodrimmer sodium is used in alignment with Schedule 4 scheduling factors of the [Scheduling Policy Framework](#) (2018).

Current scheduling status and relevant history

Astodrimmer sodium is not scheduled in the Poisons Standard and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulations

The [Australian Register of Therapeutic Goods \(ARTG\)](#) has two products that contain astodrimmer sodium (one condom lubricant and one vaginal gel). The sponsor successfully argued, based on the mechanism of action, that the vaginal gel is a medical device. The vaginal gel was approved on 24 October 2017, and is a Class IIA medical device.

Astodrimmer sodium is not in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2018](#).

In the last 2 years there have been no reported cases of adverse events related to condoms containing astodrimmer sodium in the [Database of Adverse Events Notification \(DAEN\) - Devices](#).

According to the [TGA Ingredient Database](#), astodrimmer sodium is:

- Available for use as an Active Ingredient in Devices;
- Available for use as an Excipient Ingredient in Devices; and
- Not available as an Equivalent Ingredient in any application.

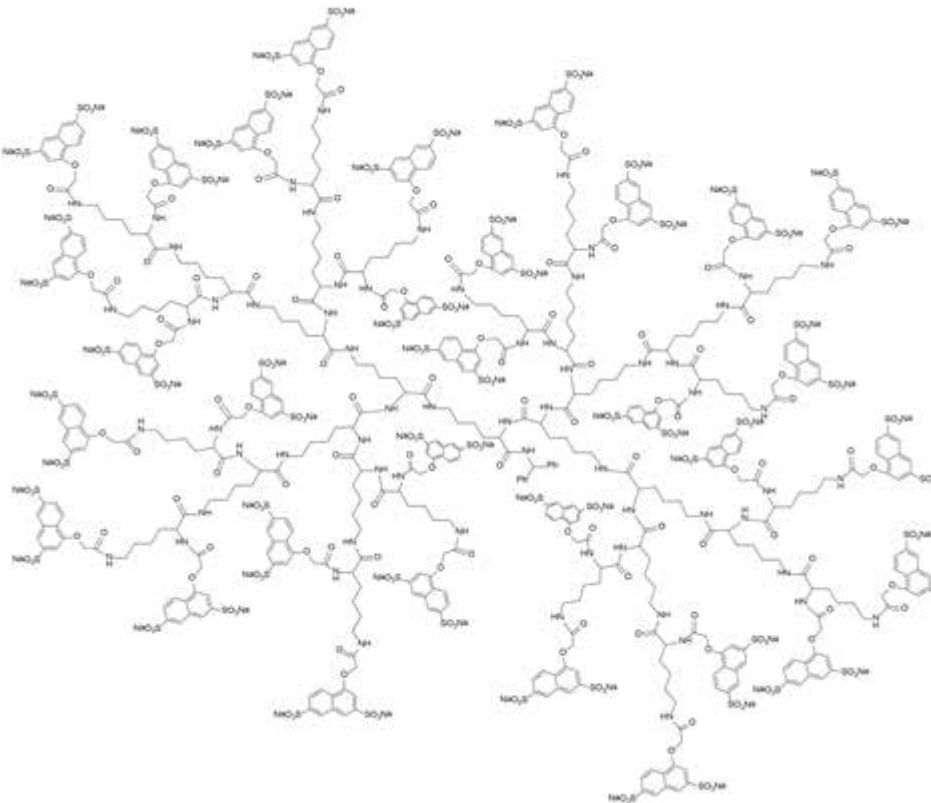
International regulations

The product in a gel formulation indicated for management of BV and sexually transmitted disease prevention, was not available for sale in any countries at the end of 2017. According to information on the sponsor's website, the vaginal gel product has been granted regulatory approval in the European Union for the treatment and symptomatic relief of BV. It is being considered for regulatory approval in the United States of America and other jurisdictions. The condom product, coated in a lubricant containing 0.5% astodrimmer sodium, is currently available for purchase in Australia and Canada.

Substance summary

Table 2.4: Chemical information for astodrimmer sodium

Property	Astodrimmer sodium
CAS number	676271-69-5
IUPAC and/or common and/or other names	Astodrimmer sodium (INN, USAN); 2, 6-Bis-{{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt; Tetrahexacontasodium N2,N6-bis{N2,N6-bis[N2,N6-bis(N2,N6-bis{N2,N6-bis[(3,6-disulfonatonaphthalen-1-yloxy)acetyl]-l-lysyl]-l-lysyl]-l-lysyl]-l-lysyl}-N1-(diphenylmethyl)-l-lysineamide; SPL7013

Property	Astodrimer sodium
Chemical structure	
Molecular formula	$C_{583}H_{577}N_{63}Na_{64}O_{287}S_{64}$
Molecular weight	16581.57 Da

Astodrimer sodium is being investigated for its potential to prevent sexual transmission of genital herpes (HSV-2), human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) including human papillomavirus (HPV), the causative agent of cervical cancer.

Mechanism of action

Astodrimer sodium is a polyanionic, polysulfonate compound that blocks the formation and disrupts pre-formed bacterial biofilms, which are important in the pathogenesis of BV.

The polyanionic surface of the highly-branched dendrimer molecule attaches to targets on viruses, thus blocking viral attachment and/or adsorption to cells to prevent infection. In standard *in vitro* assays, astodrimer sodium had antiviral activity against HIV-1, HSV-2 and HPV strains. Reduced efficacy was evident in the presence of biological fluids. Astodrimer sodium may have some antiviral activity in the cervicovaginal region but it is expected to have minimal antiviral activity in semen during use, and resistance may develop with prolonged use. In mouse and guinea pig models of genital herpes and in a macaque HIV model, astodrimer sodium prevented vaginal viral transmission in some animals at doses/concentrations exceeding those expected with the condom lubricant formulation. Astodrimer sodium gel had no impact on the vaginal or rectal flora of the southern pig-tailed monkey.

The dermal bioavailability of drug-related material in rats was 1.5% following vaginal dosing with the astodrimer sodium gel.

Acute toxicity

The no-observed-adverse-effect-level (NOAEL) and maximum non-lethal dose was 25 mg/kg intravenous (IV) in rats and rabbits. Following IV dosing, similar effects were seen in rats and rabbits with deaths, clinical signs of decreased activity and evidence of haemorrhages seen at necropsy (red discolouration of the kidneys, stomach and heart). All of these effects may be attributed to thromboembolic events. No adverse effects were seen in rats given high oral doses (≤ 1600 mg/kg). No adverse effects were seen in single dose toxicity studies in rats or rabbits following vaginal dosing of 5% astodrimer sodium gel.

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 3 months duration were performed in mice, 6 months in rats, 2 weeks in rabbits and 39 weeks in dogs using the vaginal route. Toxicity via the rectal, oral and IV routes was also examined in rats. Only limited observations were included in the IV and oral studies.

Findings in the vaginal and rectal studies were largely restricted to local reactions at the site of application. Findings associated with a gel formulation of astodrimer sodium included anal and vaginal inflammatory reactions and reductions in anal and vaginal pH (to ~ 4.5). Astodrimer sodium-associated findings included ovarian abscesses in mice (a no observable effect level (NOEL) was not established) and vaginal irritation, oedema, erosion/ulcer and/or haemorrhage in rabbits and dogs. A NOEL was not established in rabbits, while there was no evidence of vaginal irritation in dogs at concentrations $\leq 3\%$ gel. Species differences noted in local effects of vaginal dosing with the gel was attributed to differences in vaginal structure.

Systemic effects following repeated vaginal dosing were only seen in rabbits – thrombosis in the vagina with thrombi evident in multiple organs of animals that died prematurely. These systemic effects are likely a result of severe local (vaginal) irritation and damage. Rabbits are generally more sensitive to vaginal irritants than human subjects. The NOEL for systemic effects in rabbits was 1% astodrimer sodium gel (2.9 mg/kg/day) suggesting thrombosis may not be seen in human subjects.

Astodrimer sodium is considered to have a low genotoxic potential. No treatment-related increase in tumour incidence was observed in mice or rats in 2-year vaginal carcinogenicity studies at very high doses.

No adverse effects on female fertility, embryofetal development or pre/postnatal development were evident in rats following vaginal dosing. In the rabbit embryofetal development study there was an increased incidence of abortions and early delivery with the 1% astodrimer sodium gel. These effects were considered to be secondary to maternotoxicity (vaginal irritation and thrombosis) rather than a direct drug-related effect.

There was no evidence of delayed contact hypersensitivity in a standard assay in guinea-pigs using 4% astodrimer sodium in the induction phase ($3 \times$ oh occluded dermal applications) and challenging with 2% astodrimer sodium 14 days after induction. No gross indications of penile irritation were seen in male dogs following exposure to 3% astodrimer sodium gel.

Pre-meeting public submissions

One (1) public submission was received before the first closing date in response to an [invitation published on 12 April 2018](#) under regulation 42ZCZK of the Regulations. The submission opposed the proposal.

The main points provided in opposition of the amendment were:

- The proposal to create a new schedule 4 entry for astodrimmer sodium does not relate to any risk of poisoning, misuse, and abuse for astodrimmer sodium, or other relevant scheduling factors.
- Systemically absorbed antibiotics are currently the only available therapy for BV. Antibiotics are prescription medicines that require medical management due to the potential development of resistant bacteria. In contrast, astodrimmer sodium has a unique non-antibiotic mechanism of action, it is not absorbed into the bloodstream, has a very benign safety profile, and does not cause spontaneous development of resistant bacteria. Astodrimmer sodium provides a low-risk, non-antibiotic, and non-prescription alternative for women to treat their BV.
- BV is an imbalance in the normal vaginal flora and not an infection caused by a specific pathogen. It is usually a non-serious condition, and treatment of asymptomatic BV is typically not required. BV does not require medical diagnosis, management and monitoring. The need for a woman with BV to be treated via involvement of a doctor is because there are no non-antibiotic treatments.
- Self-treatment of BV does not pose a risk of masking another more serious condition and there is no scientific evidence that repeat episodes of BV are caused by an underlying condition (e.g. diabetes).
- Non-prescription treatments for the more complex vaginal yeast infection are currently available in Australia. Vaginal yeast infection (candidiasis) is an infection caused by *Candida albicans*. Vaginal candidiasis has the potential to be misdiagnosed, and repeated episodes of candidiasis may be indicative of a more serious condition, such as diabetes or compromised immunity.
- Research indicates that only a small proportion of women with BV are attending general practitioners (GPs) or specialists. Patients with BV prefer to present to pharmacies as an initial point of contact, and there is a large degree of dissatisfaction with currently available therapies.
- Many women's experiences with the clinical management of BV through primary care providers (GPs) are negative; research shows that clinicians frequently fail to diagnose or misdiagnose BV, and are often insensitive when treating patients with the condition.
- Toxicity
 - The clinical safety and efficacy of astodrimmer sodium has been investigated in 11 completed clinical studies involving more than 2000 patients, including four global Phase 3 studies.
 - Astodrimmer sodium is not systemically absorbed following topical, e.g. vaginal, application. Given this lack of absorption, the product represents a negligible risk of systemic side effects or interaction with food, alcohol, or other medical products, and very low to non-existent risk of dependency, misuse, abuse or illicit use.
 - There was no evidence of any teratogenic, mutagenic or carcinogenic effects of astodrimmer sodium.

- Astodrimmer sodium is also used as an ingredient in the lubricant of a condom product where its intended purpose is to inactivate viruses that may be sexually transmitted. The condom product with astodrimmer sodium has been sold in Australia since 2014 and Canada since 2017. There have been no complaints or safety issues associated with use of astodrimmer sodium in the condom product. Further, there is no risk of confusing the condom product containing astodrimmer sodium with the gel product for BV.
- Access
 - A decision to create a Schedule 4 entry for astodrimmer sodium based on the requirement that BV needs medical diagnosis and intervention would be inconsistent with the way vaginal candidiasis is currently treated by the regulator and managed in practice. It would create a precedent for women that any future product for BV, regardless of the risk/benefit profile of a particular product, must also be Schedule 4 and require a visit to a medical practitioner to obtain a prescription, where proper examination and correct diagnosis are not always guaranteed, and patient satisfaction is low.
 - Creating a new Schedule 4 entry for astodrimmer sodium would deny women's preference to access treatment for BV without a doctor's visit, and deprive Australian women of the ability to effectively manage this embarrassing and recurring condition.
 - While women may inaccurately self-diagnose in some cases, this risk must be considered in the context of and given equal weight as published research showing that physicians misdiagnosed BV in 61.3% of cases, and that the rate of misdiagnosis of vaginal candidiasis was even higher (77.1%).⁵¹ In addition, studies have shown that women with recurrent BV commonly reported primary care providers had often confused BV for candidiasis, with a number indicating they had been diagnosed and treated for candidiasis without further testing, or had been tested and/or treated for chlamydia or other sexually transmitted infections (STIs) without being tested for BV.⁵²
- The available evidence on women's preferences and practices as reported in the scientific literature, and overseas experiences with BV products sold direct-to-consumers without prescription in comparable markets such as the UK, confirm the ability of women to self-select treatment in the absence of harm.
- Women are capable of being informed and self-selecting products, which have appropriate labelling, packaging and the opportunity for point of sale advice, for the treatment of BV. Recent TGA-approval of restricted advertising representations for the product containing astodrimmer sodium is consistent with this view.
- Mistreatment
 - The potential for astodrimmer sodium to be used to treat a condition other than BV is mitigated by the recently approved restricted representations and required advisory statements for the gel product, including the requirement for an accurate description of BV in the product packaging and instructions for use.
 - The benign safety profile of astodrimmer sodium, there is no added risk of harm from exposure to the product for women who may not have BV.
 - Research shows that women with BV are already treating with over-the-counter therapy for candidiasis because it is a therapy that is readily available without prescription.⁵² The

⁵¹ Schwartz A, Taras D, Rusch K *et al.*, Throwing the dice for the diagnosis of vaginal complaints? *Ann Clin Microbiol Antimicrob* 2006;5(4): doi:10.1186/1476-0711-5-4.

⁵² Bilardi JE, Walker S, McNair R *et al.*, Women's management of recurrent bacterial vaginosis and experiences of clinical care: A qualitative study. *PLoS One* 2016;11(3):e0151794.

availability of a product specifically for BV will reduce the potential for off-label treatment with an inappropriate product to occur.

- The consequence of inaccurate self-diagnosis and use of astodrimmer sodium would be that a woman treats a condition that is not BV, and delays treatment of another condition for a short period of time. Women who have shown health-seeking behaviour by choosing a therapy for the condition are likely to seek further treatment if their condition is not resolved, minimising the delay in treatment.
- Schedule 2 is more appropriate (unscheduled preferred) with appropriate reference to Appendix F statements (E.g. 64).

Joint ACMS-ACCS advice

The committee recommended that new Schedule 3 and Appendix F entries be created for astodrimmer sodium as follows:

Schedule 3 – New Entry

ASTODRIMER SODIUM except in a condom lubricant.

Appendix F – New Entry

ASTODRIMER SODIUM

Warning statements: 63 (See a doctor if you are pregnant or diabetic), 64 (See a doctor if not better after 7 days), 69 (If symptoms recur within two weeks of completing the course, consult a doctor), 75 (Do not use for more than 7 days unless a doctor has told you to).

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

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

The reasons for the advice included:

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

- Minimal risk. Low toxicity. Evidence of efficacy.
- The risks of remaining unscheduled are the potential for self-treatment without health professional assessment to exclude STI.
- Benefits of product are a non-antibiotic option for the treatment of bacterial vaginosis. Side effects are minimal and so compliance is expected to increase for successful treatment.

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

- Bacterial Vaginosis (BV).
- Bacterial vaginosis is a very common condition in women, with prevalence estimates of 10-50%. It commonly recurs after treatment. Symptoms of such a medical condition require health professional assessment.

(c) the toxicity of a substance:

- Low.
- Minimal systemic toxicity risk, local irritant/inflammatory effects.

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

- Vaginal gel. A number of mandatory labels have been proposed including the requirement for an accurate description of BV in the product packaging and instructions for use.

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

- Improved public awareness of condition if available OTC but very recently launched product worldwide with no post-marketing surveillance. May be suitable for future Schedule 2 listing but needs further evaluation and better data on consumer diagnostic accuracy/missed diagnosis of STI and access to diagnostic self-testing.
- Advertising appropriate in alignment with vaginal fungal treatments.