Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Notice of interim decisions to amend (or not amend) the current Poisons Standard

14 March 2025

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Contents

Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary of the Department of Health and Aged Care responsible for scheduling of medicines and chemicals (the **Delegate**)[1] under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[2] under subdivision 3D.2 of the Regulations in November 2024.
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before 4 April 2025.

Submissions should be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

Defined terms

In this notice the following defined terms are used in addition to those above:

- the *Therapeutic Goods Act 1989 (Cth)* (the **Act**)
- the Scheduling Policy Framework 2018 (the **SPF**)
- the Scheduling handbook: Guidance for amending the Poisons Standard (the **Handbook**), and
- the Therapeutic Goods Administration (the **TGA**).

Note: additional terms are also be defined for individual decisions.

[1] For the purposes of s 52D of the *Therapeutic Goods Act 1989* (Cth)

[2] Established under sections 52B and 52C of the *Therapeutic Goods Act 1989* (Cth).

Interim decision on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #46, November 2024)

Interim decision in relation to *Atropa belladonna*

Proposal

The proposal is to remove the Pharmacy medicine (Schedule 2) entry for *Atropa belladonna* (belladonna) from the Poisons Standard, making all preparations a Prescription Only medicine (Schedule 4). *Atropa belladonna* is included in Schedule 2, Schedule 4 and Appendix G in the current Poisons Standard.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard as follows:[3]

Schedule 4

ATROPA BELLADONNA (belladonna) **except** when included in Schedule 2.

Schedule 2 – Amend Entry

ATROPA BELLADONNA (belladonna):

(a) for external use in preparations containing 0.03% or less of total solanaceous alkaloids; or

(b) for oral use in adults and children 6 years of age and over:

(i) in undivided preparations containing 0.03% or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(ii) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit, when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

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ATROPA BELLADONNA

Cross reference: BELLADONNA

Schedule 4

Schedule 2

Appendix G, clause 1

Appendix G – Dilute preparations

Clause 1, Item 6

ATROPA BELLADONNA is exempt at or below 300 micrograms per litre or kilogram.

[3] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The 6 public submissions, all with a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**)
- The advice received from the 46th meeting of the Advisory Committee on Medicines and Scheduling (the **Committee**)
- The SPF
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entry for *Atropa belladonna* be amended as follows:

Schedule 4

Schedule 4

ATROPA BELLADONNA (belladonna) **except** when included in Schedule 2.

Schedule 2 – Amend Entry

ATROPA BELLADONNA (belladonna):

(a) for external use in preparations containing 0.03% or less of total solanaceous alkaloids; or

(b) for oral use in patients over 6 years:

(i) in undivided preparations containing 0.03% or less of total solanaceous alkaloids when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or

(ii) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit, when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

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

The reasons for the advice included:

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

Risks:

– Narrow therapeutic index.

– Anticholinergic effects with a wide range of side effects.

– Signs and symptoms of toxicity include erythematous flushed skin, dry skin, dry mouth, mydriasis, tachycardia, urinary retention. gastrointestinal ileus, raised temperature, agitation, drowsiness, floppiness, poor feeding and occasionally seizures.

– Onset of toxicity is usually within 30 minutes to 4 hours; symptoms may be significantly delayed or prolonged due to decreased gastric motility and may vary due to frequency of dosing.

– Natural plant growth variation and extraction methods may result in variability in concentration when used in compounded medicines.

Benefits:

– Although not a recommended treatment, has historically been used for colic.

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

– Has been used in Australia for children in preparations for ‘colic’ although safer treatments with a more favourable risk-benefit profile are available as alternatives.

– Available unscheduled in homeopathic topical preparations for muscle and joint pain and in dry cough formulations.

c) the toxicity of a substance

– Adverse event reporting over the last 2 years identifies concerns particularly in children under 6 years of age. Potential for carers to not recognise signs of overdose as they can be similar to a dose working as intended (reduction in child restlessness and crying).

– The time to effect is wide ranging and second and subsequent doses may occur before the first dose takes full effect, resulting in repeated dosing resulting in overdose.

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

– Dosages vary, including various homeopathic dilutions.

– There are 8 products listed on ARTG: 4 topical creams/gels, 1 teething gel, 1 cough mixture, 2 homeopathic tablets. Of these 8 products, *Atropa belladonna* is included in 7 as a homeopathic ingredient and in one cream as an herb extract liquid concentrate for topical use. The only oral liquid as a homeopathic product on the register is for dry cough.

e) the potential for abuse of a substance

– There is a potential for misuse or inadvertent mis-dosing errors in children where carers may be unaware of the risks involved.

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

– There should be consideration for alignment of other constituent alkaloid entries in the Poisons Standard (including hyoscine, hyoscyamine and atropine entries) with any amendments made to the *Atropa belladonna* entries.

– There is a lack of public awareness of the potential risks of plant-based products.

– There should be consideration for clarification of the Appendix G entry to consider alkaloid content in alignment with the Permissible Ingredients Determination.

Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I have made an interim decision to amend the Schedule 2 entry for *Atropa belladonna*.

I have considered the 6 public submissions received during the pre-meeting consultation period: 4 were supportive, 1 was partially supportive, and 1 opposed the proposal. All the submissions provided written justifications.

The supportive justifications highlighted that *Atropa belladonna* has limited therapeutic use, contains high amounts of toxic tropane alkaloids such as atropine, scopolamine, and hyoscyamine and can be toxic when used inappropriately. The proposal to classify belladonna as a prescription medicine would require an herbal medicine practitioner to work with a medical doctor to support patient care.

The partially supportive submission acknowledged that the proposed amendment would reduce the possibility of misuse and adverse events, but also raised concerns about access, healthcare burden, and potential market issues.

The opposing submission highlighted the low potential for harm from belladonna present in homeopathic preparations and topical creams and a lack of definitive association with belladonna for most of the reported adverse events. Scheduling belladonna preparations as prescription only medicines will limit consumer access and severely impact the traditional medicine industry.

In relation to sections 52E(1)(b) and (d) of the Act, currently there are only 8 medicines the Australian Register of Therapeutic Goods (ARTG) containing *Atropa belladonna* as an active ingredient. All the 8 are listed medicines of which 4 are for topical applications and rest are oral medicines.

There is insufficient information on safe paediatric doses for preparations containing belladonna tincture. The current Poisons Standard entry, last considered in 2006, focused on concentration cut-offs for harmonisation with New Zealand rather than on paediatric dose considerations.

Regarding s 52E(1)(c) of the Act, I note that in August 2024, there were 62 reports of adverse events for products containing *Atropa belladonna* as an active ingredient on TGA's Database of Adverse Event Notifications (DAEN). From the beginning of 2023, 49 adverse events have been reported where belladonna was considered the main ingredient that caused the event. Twenty-one of these events were in children under 3 years of age. While the age was not specified for the remaining 28 events, all were using a 'colic' product intended for infants and therefore can be assumed to have been used in children under 6 years of age.

I note that for belladonna the onset of toxicity is usually within 30 minutes to 4 hours but can be significantly delayed due to decreased gastric motility. This may increase the risk of additional dosage leading to an overdose. Further, exhaustion in parents of children with colic symptoms may also increase the risk of incorrect dosing in infants.

I am also concerned about the manufacturing and compounding processes of these products, as the alkaloid levels can vary naturally as well as due to differences in extraction processes. Additionally, I agree with the Committee that while the popularity of natural remedies has increased, there is a lack of public awareness and knowledge about the risks associated with plant-based products. Considering the recent, high incidence of adverse events in children, risk of inadvertent overdosing, lack of consumer knowledge of possible toxic effects and the perceived safety of belladonna as a plant-based product, I have decided to limit the use of oral preparations to adults and children over 6 years of age.

I have also amended the wording suggested by the Committee for consistency with other entries in the Poisons Standard that impose similar age restrictions.

Further, considering the recent increase in adverse event reports particularly in children under 6 years of age, I have decided on an immediate implementation date of 1 June 2025.

Proposed implementation date

1 June 2025

Interim decisions on proposed amendments referred to the Advisory Committees on Medicines and Chemicals Scheduling in joint session (ACMS-ACCS #38, November 2024)

Interim decision in relation to ethylene oxide, propylene oxide, epichlorohydrin

Proposal

The proposal is to amend the current scheduling of ethylene oxide, propylene oxide and epichlorohydrin. The applicant proposed preparations containing less than 0.002% (20 ppm) of ethylene oxide, propylene oxide and epichlorohydrin to be exempted from the Dangerous Poisons (Schedule 7) entries for these substances.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to ethylene oxide, propylene oxide and epichlorohydrin.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to ethylene oxide, propylene oxide and epichlorohydrin (the **Application**)
- The 2 public submissions, both including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**).
- The advice received from the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**)
- Subsection 52E(1) of the Act, in particular (a) 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
- The Therapeutic Guidelines
- The Australian Medicines Handbook
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee considered that there is not enough data to justify exempting products containing 20 ppm or less of ethylene oxide, propylene oxide, and epichlorohydrin from scheduling as proposed by the applicant. However, the Committee recommended that the Schedule 7 entries for ethylene oxide, propylene oxide, and epichlorohydrin be amended to include an exemption cut-off of 0.001% (10 ppm) or less for each substance provided that the Delegate is satisfied that there are no risks to

human health associated with products containing these substances at this concentration. The recommended amendments are as follows:

Schedule 7 – Amend Entry

ETHYLENE OXIDE **except** in preparations containing less than 0.001% of ethylene oxide

PROPYLENE OXIDE **except** in preparations containing less than 0.001% of propylene oxide

EPICHLOROHYDRIN **except** in preparations containing less than 0.001% of epichlorohydrin

Such amendments will be consistent with the general exemption for poisons listed only in Schedules 1 to 6 when present at a concentration not exceeding 10 mg per litre or 10 mg per kilogram (0.001% or 10 ppm) and will allow trace amounts of ethylene oxide, propylene oxide, and epichlorohydrin to be present in various preparations as genuine unavoidable impurities.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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.

The reasons for the advice included:

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

Risks:

- Manufacturing risks are mitigated through workplace controls, but the consequences of residual amounts of these substances, particularly in personal cleaning products are not well understood.
- Higher concentrations of these substances pose a clear risk to human health.

Benefits:

- Surfactant preparations have a wide range of uses in medicines, consumer products, AgVet and industrial products.

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

- Manufacturing usage: many types of products ranging from epoxy resins employed in a variety of manufacturing sectors, to detergents (surfactants), personal care products and munitions.
- Widespread throughout many sectors including health, personal care, and food processing

c) the toxicity of a substance

- Lack of data to assess the risks of these chemicals when present in low concentrations, particularly when used in combination in products.
- While specific data are limited, preparations containing levels of ethylene oxide, propylene oxide, and epichlorohydrin below the proposed cutoff do not appear to pose a risk commensurate with the Schedule 7 (or any other schedule) scheduling factors.

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

- These products exist as impurities in a wide variety of applications.

- Example products with residual levels of ethylene oxide
    - Cleaning products: 1-5 ppm
    - Toothpaste: less than 1 ppb
    - Personal care products: less than 1 ppb
    - Air fresheners: less than 1 ppb
    - Therapeutic goods: less than 1 ppb.
- Propylene oxide is a raw material used in the manufacture of chemical derivatives, a stabiliser and a solvent.
- Epichlorohydrin is a chemical intermediate used in a variety of applications, including epoxy resins, textiles, paper products, inks, dyes, automotive and aircraft parts, biocides, personal care products, and ion-exchange resins.

e) the potential for abuse of a substance

- Nil

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

- Due to the improvements in technology for detecting chemicals, the threshold of detection of these substances is below the level that industry can practically reduce the concentration to in manufacturing processes.
- The level of evidence for the risks of low levels of these substances on human health has also improved.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to not amend the current scheduling of ethylene oxide, propylene oxide and epichlorohydrin to exempt preparations containing trace amounts (less than 0.001% or 10 ppm) of these 3 substances to be exempted from Schedule 7.

I agree with the Committee that due to the similarity of chemical structures and scheduling history of ethylene oxide, propylene oxide, and epichlorohydrin, the 3 substances are appropriate to be considered together for scheduling. I broadly agree with the Committee's findings on the relevant provisions of section 52E of the Act. However, I consider that the available information does not support the assertion that preparations containing 10 ppm or less of these substances pose no or very low risks to human health.

I have considered the 2 public submissions received during the pre-meeting consultation period. Both the responses were fully supportive of the proposal and provided written justifications. One submission further proposed that substances for workplace use should be exempted from Schedule 7 obligations at concentration of less than 1,000 ppm as this is below any required hazardous classifications under the Global Harmonised System (GHS) framework and are considered low risk. Such a proposal in beyond the scope of the amendments under consideration.

In considering s 52E(1)(a) and (b) of the Act, I note that ethylene oxide, propylene oxide and epichlorohydrin in surfactant preparations are widely uses in medicines, consumer products, agvet and industrial products. Ethylene oxide is also used for sterilising medical instruments and supplies that cannot withstand heat treatment, and fumigation of food, paper, fabrics, and wooden and leather products. I agree with the Committee’s view that while higher concentrations of these substances pose a risk to human health, manufacturing risks should be mitigated through workplace controls. However,

the risks from exposure to residual amounts of these substances as impurities in products, particularly in personal care products, have a degree of uncertainty.

Ethylene oxide is an established carcinogen in laboratory animals. Several long-term animal studies reported increased carcinogenesis when animals were exposed to ethylene oxide via oral gavage (increased squamous cell carcinomas in rats at 7.5 mg/kg bw/day) or inhalation (various cancers and benign tumour formation in rats exposed to 10-100 ppm ethylene oxide for 5-7 hours/day, 5 days a week for 2 years).[4] While there is some uncertainty about the carcinogenic nature of ethylene oxide in humans, a genotoxic mode of action for carcinogenicity cannot be ruled out for epichlorohydrin.[5,6]

Based on the available evidence, the International Agency for Research on Cancer (IARC) has classified ethylene oxide as Group 1 (carcinogenic to humans) carcinogens, epichlorohydrin as Group 2A carcinogens (probably carcinogenic to humans) and propylene oxide as Group 2B carcinogen (possibly carcinogenic to humans).[7] Safe Work Australia (SWA) also considers ethylene oxide, propylene oxide and epichlorohydrin to have carcinogenic potential for humans (Category 1B of the GHS Classification).[8] Since 2003, FSANZ has disallowed the use of ethylene oxide as a treatment for foods sold in Australia (previous residue limits were 20 ppm).[9] I note that there are several substances listed in the Permissible Ingredient Determination that limit ethylene oxide to either below the limit of detection, or 1 ppm.

While I agree with the Committee that the available acute toxicity data for ethylene oxide, propylene oxide and epichlorohydrin allow for exemption from Schedule 7 classification, all the 3 substances are potentially carcinogens. Carcinogenesis may occur without any observed acute toxic effects and risk characterisation should consider the adequacy of any existing control and the feasibility and practicability of further specific measures for each scenario.

The exemption cut-off of 10 ppm suggested by the Committee is based on the general cut-off applicable to a substance included in Schedules 1 to 6, provided the substance is not included in Schedules 7 or 8 (section 11(d) of the Poisons Standard). I acknowledge that ethylene oxide, propylene oxide and epichlorohydrin can be present in various consumer products as unavoidable impurities. Due to the current scheduling provisions, industry reduces the residual concentration of these substances to the lowest practical limit that is technologically possible. However, advances in analytical methods means that detection limits continue to improve.

A recent systematic review on ethylene oxide suggested ‘evidence of no association between ethylene oxide and stomach cancer, breast cancer and lymphohematopoietic malignancies at human relevant exposures’.[10] However, SWA considers ethylene oxide to be a non-threshold based genotoxic carcinogen.[11] Further, the 8-hour time weighted average exposure permissible for workers for propylene oxide and epichlorohydrin were estimated to be 2 ppm and 0.5 ppm, respectively.[12] The amount of these substances present as impurities in various products varies considerably and can range from less than 1 ppb in toothpastes to 5 ppm in cleaning products. Some of the consumer products are rinse-off while others are leave-on, increasing exposure through prolonged skin contact. Use of multiple products with one or more these substances can also increase the cumulative exposure.

The key concern, in evaluating the potential risks to human health, is what would the risks to human health be from increased exposure to the substances resulting from higher-concentration exemption cut-offs in the Poisons Standard. In view of the carcinogenic nature of ethylene oxide, propylene oxide

[4] Oxirane: Human health tier II assessment, National Industrial Chemicals Notification and Assessment Scheme, 2014.

[5] European Union Risk Assessment Report Methyloxirane (propylene oxide). Volume 23, 2nd Priority list (2002).

[6] Oxirane, (chloromethyl)-: Human health tier II assessment, National Industrial Chemicals Notification and Assessment Scheme, 2013.

[7] IARC Monographs on the Identification of Carcinogenic Hazards to Humans (accessed 21 February 2025)

[8] Safe Work Australia Hazardous Chemical Information System (accessed 21 February 2025)

[9] Ethylene oxide | Food Standards Australia New Zealand

[10] Lynch HN, Kozal JS, Russell AJ, Thompson WJ, Divis HR, Freid RD, Calabrese EJ, Mundt KA. Systematic review of the scientific evidence on ethylene oxide as a human carcinogen. Chem Biol Interact. 2022 Sep 1;364:110031. doi: 10.1016/j.cbi.2022.110031.

[11] Workplace exposure limits for airborne contaminants, Safe Work Australia (2024).

[12] Workplace exposure limits for airborne contaminants, Safe Work Australia (2024).

and epichlorohydrin and the lack of high-quality information to support that there is no risk to human health from exempting all products containing 10 ppm or less of these 3 substances, I have decided not to amend the scheduling of these 3 substances at this time.

Interim decision in relation to Astodrimer sodium

Proposal

The proposal is to classify astodrimer sodium vaginal gels for the treatment, relief and prevention of bacterial vaginosis (BV) as Pharmacy medicines (Schedule 2). These preparations are currently a Pharmacist Only medicine (Schedule 3). The application also proposed an amendment to the Appendix H entry that would permit advertising of all Schedule 3 preparations of astodrimer sodium. The current Appendix H entry only allows advertising of preparations for the treatment and relief of bacterial vaginosis and prevention of recurrent bacterial vaginosis (RBV).

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, regarding the proposed amendments, made an interim decision to not amend the current Poisons Standard in relation to astodrimer sodium.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to astodrimer sodium (the **Application**)
- The 12 public submissions, including 11 with a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**)
- The advice received from the 46th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The SPF
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard classification for astodrimer sodium remains appropriate. The Committee also recommended that the Appendix H entry should not be amended.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) 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.

The reasons for the advice included:

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

Risks:

- Astodrimer sodium has shown limited, local and self-limiting adverse events. The risk profile of the substance is deemed to be low risk and well tolerated.
- 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 warranted to exclude the possibility of misdiagnosis.

Benefits:

- Astodrimer sodium is a polyanionic dendrimer that blocks attachment of bacteria to cells, preventing formation of bacterial biofilms, which are central to the pathogenesis of bacterial vaginosis (BV).

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

- Astodrimer sodium 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. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine and to reduce the risk of misdiagnosis and confusion with other conditions.

c) the toxicity of a substance

- Astodrimer sodium is of low toxicity, with minimal risk of systemic toxicity or local irritant/inflammatory effects. These characteristics are appropriate for an over-the-counter product.

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

- It is available for treatment of BV as an aqueous-based, vaginal gel containing 1% w/w astodrimer sodium.

e) the potential for abuse of a substance

- Astodrimer sodium is not systemically absorbed; therefore, dependence, misuse or overdose of astodrimer sodium is not expected and has not been reported.

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

- Vaginal candidiasis has a similar disease risk profile to bacterial vaginosis with less serious complications, and all currently marketed vaginal candidiasis treatments are at least Pharmacist only medicines (Schedule 3).

Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I have made an interim decision to not amend the Poisons Standard with regards to astodrimer sodium.

I have considered the 12 public submissions received during the pre-meeting consultation period. Interested parties were given the choice to indicate their support or opposition to the proposed amendments with or without providing a written component. Seven of the supportive submissions provided written responses highlighting astodrimer sodium as a safe and effective non-antibiotic treatment option for BV and prevention of RBV. Increasing access to an efficacious product for the treatment of a common condition as BV is in the interest of public health. It also poses no risk of contributing to antibiotic resistance.

The partially supportive submission proposed that astodrimer sodium be included in both Schedule 2 and Schedule 4 of the Poisons Standard and urged consideration of astodrimer sodium to be a prescription medicine for BV treatment. Inclusion in Schedule 2 will allow better access for effective medication against BV while inclusion in Schedule 4 will facilitate products to be listed in Pharmaceutical Benefits Scheme where reasonably priced medically supervised treatment is needed and appropriate, for example for treatment of COVID-19 in generally healthy people under 70 years of age.

The 3 opposing submissions acknowledged the safety profile of astodrimer sodium being commensurate with Schedule 2 but raised concerns regarding the risk of misdiagnosis of BV by the patient. Consultation with a pharmacist is likely to provide appropriate guidance and timely referral to a doctor. Additionally, the required advisory statements for labelling for astodrimer sodium vaginal gel products are based on the Schedule 3 supply restrictions in Australia.

BV is an imbalance in the normal vaginal flora and not an infection caused by a specific pathogen. It is a very common condition in women, with an estimated global prevalence of 23-29% among women of reproductive age.[13]

Astodrimer sodium is a highly branched molecule that has a polyanionic surface which binds to virus outer coat proteins and blocks virus attachment and/or adsorption to cells to prevent infection. It is an option for the treatment of BV, common sexually transmitted infections (STIs) including HIV, HSV and HPV, and cold and respiratory viruses. With reference to s 52E(1)(b) and (d) of the Act, I note that astodrimer sodium is available for the treatment of BV as a vaginal gel containing 1% w/w astodrimer sodium.

With regards to s 52E(1)(a) and (e) of the Act, while astodrimer sodium poses a low risk of toxicity and is not systemically absorbed, I agree with the concerns expressed by the Committee around the risks of misdiagnosis and inappropriate use of the substance for BV. The clinical presentation of BV often overlaps with other conditions, including vulvovaginal candidiasis (thrush), STIs and urinary tract infections (UTI). Self-testing devices do not eliminate the potential for misdiagnosis and consumers may misinterpret their symptoms and incorrectly self-diagnose conditions such as STIs or UTIs to be BV. Given the overlapping symptoms, and potential consequences of misdiagnosis, treatment of BV requires health professional intervolvement. Further, vaginal candidiasis has a similar disease risk profile to BV with less serious complications and all the currently marketed vaginal candidiasis treatments are at least Pharmacist only medicines (Schedule 3).

In considering s 52E(1)(f) of the Act, references to BV and RBV in advertising about therapeutic goods are considered as restricted representations. This is because BV and RBV are considered as serious forms of a disease, condition, or ailment that require diagnosis or treatment or supervision by a suitably qualified health practitioner.

In summary, diagnosis of BV is substantially safer with pharmacist oversight to mitigate the risk of consumer misdiagnosis and provision of appropriate advice for the prevention of BV. I agree with the advice of the Committee that the current scheduling of astodrimer sodium remains appropriate, and no changes should be made to its scheduling.

[13] Bacterial vaginosis, World Heath Organisation (page accessed on 24 February 2025)

Interim decision in relation to *Symphytum officinalis* (comfrey)

Proposal

The proposal is to amend the Schedule 5 entry for *Symphytum officinalis* (comfrey) to allow dermal preparations for therapeutic or cosmetic use to be unscheduled when containing concentrations of 20% or less of comfrey. Comfrey is captured in the current Poisons Standard as a Caution (Schedule 5) substance for dermal therapeutic or dermal cosmetic use, and Schedule 10 for all other preparations for human or animal use. Schedule 5 preparations containing comfrey are also required to carry safety directions regarding not using on broken skins or under occlusive dressing.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to *Symphytum officinalis*.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to comfrey (the **Application**)
- The 6 public submissions, with 5 including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**)
- The advice received from the 38th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the **Committee**)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entry for comfrey remains appropriate.

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

The reasons for the advice included:

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

Risks:

– The primary risks associated with comfrey preparations is from toxicity arising from naturally occurring pyrrolizidine alkaloids (PAs) that are known to be hepatotoxic and mutagenic.

- There are several documented cases of human toxicity and death from oral comfrey and/or PAs, including perinatal death from maternal use.
- There is evidence of non-negligible risks related to toxicity. Most of the data is from short-term use and the data from long-term use is less established.
- There is low to minimal risk of dermal formulations of comfrey with appropriate short-term use, as PAs are poorly absorbed through intact skin and not bio-transformed into toxic metabolites by skin bacteria.
- There is some evidence that toxic PAs can penetrate human skin at low concentrations.

Benefits:

- Comfrey preparations have been used in herbal medicine for centuries to treat a range of conditions such as bruises, osteoarthritis, sprains, muscle/tendon damage and fractures.
- Topical cream formulations have been available for many years as a complementary medicine.
- Biological activity of comfrey is proposed to be linked to natural anti-inflammatory compounds and other agents associated with skin repair and healing.
- There is some efficacy data from clinical studies and some clinical evidence of efficacy. A Cochrane Review[14] of herbal medicine for low back pain did not find sufficient evidence for use.

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

- Comfrey preparations are commonly used in herbal and complementary remedies for a range of conditions from bruises to muscle damage and osteoarthritis. This may increase systemic exposure to PAs.
- Traditional use includes application for wound healing which may increase exposure to PAs.
- Are also used in cosmetic products; however, the usage volume of these in Australia is unknown.
- There is no established seasonal use pattern for preparations containing comfrey.

c) the toxicity of a substance

- Comfrey is toxic primarily due to the presence of naturally occurring pyrrolizidine alkaloids (PAs), which is known to cause severe liver damage in humans and animals when ingested.
- Both acute and chronic liver toxicity has been documented with ingestion, along with risk of carcinogenicity when ingested.
- Mutagenic effects have also been documented.
- The primary target organ for toxicity is the liver followed by the lungs. Chronic exposure can also lead to cumulative liver damage.
- The potential toxicity of dermal applications is uncertain. Toxicity associated with dermal preparations is anticipated to have lower levels of absorption, under some conditions.
- Topical application has lower absorption across skin and less opportunity for liver metabolism to pyrrole compounds.

[14] Oltean, Robbins, van Tulder, Berman, Bombardier, Gagnier. Herbal medicine for low-back pain. Cochrane Database of Systematic Reviews 2014, Issue 12. DOI: 10.1002/14651858.CD004504.pub4

- Toxicity is increased when used in children, on compromised or broken skin, or with prolonged use over large areas.

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

- Three registered topical products are listed on the ARTG.
- Comfrey ointments, creams, poultices, and liniments are made from the fresh or dried herb, leaf, or root of comfrey species.
- Typical concentrations of preparations vary from 5 to 20% comfrey. However, levels of toxic PAs in these preparations can vary considerably.
- Some newer manufacturing processes claim to be able to reduce the levels of toxic pyrrolizidine alkaloids significantly which can mitigate risks associated with accidental misuse or overuse.
- Variable formulations can increase the risk of higher amounts of PAs being absorbed. Formulation variability could relate to excipients and to use of PA depleted versus non-depleted Symphytum extracts.
- Comfrey is mentioned in Appendix F of the Poisons Standard, which mandates specific warning statements on product labels:
    - Warning 31: “Do not use on broken skin”
    - Warning 32: “Do not use under occlusive dressing”

e) the potential for abuse of a substance

- There is low potential for abuse with currently available formulations.

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

- Lack of compliance with using the substances in the way it is intended.
- Consider warning labels:
    - Risks in breast feeding and pregnancy
- Consider advising current sponsors of comfrey topical therapeutic products that their labels are non-compliant with the Poisons Standard (no signal heading or signal heading in incorrect location and lettering appears too small).
- Note that current scheduling does not restrict where the product can be sold.

Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I have made an interim decision to not amend the Poisons Standard with regards to comfrey. In making this decision I have balanced the potential benefits of increasing access to comfrey against the potential risks explained below.

I have considered the 6 public submissions, 5 supportive and 1 partially supportive, received during the pre-meeting consultation period. Interested parties were also given the choice to select from options to indicate their support or opposition to the proposed amendment without providing a written component. Four of the supportive submissions and the partially supportive one provided written justifications.

The supportive submissions commented on comfrey's use in traditional medicine as a topical agent for joint and musculoskeletal conditions and considered the risks in dermal preparations containing less than 20% comfrey to be sufficiently safe as to not require warning statements. Two of the supportive submissions further stated that low concentrations of comfrey in dermal preparations pose no risk of hepatic or pulmonary toxicity due to small quantities of PAs in the product. Submitters also noted that the proposed scheduling would align with international regulations.

The partially supportive submission agreed that the proposal would align with international regulations for traditional medicine uses but expressed concerns about the risks associated with PAs and the potential for adverse events. The submission further noted the lack of robust clinical data and advocated for a cautious and considered approach.

In considering s 52E(a) and (b) of the Act, I note that topical comfrey preparations are used in traditional medicine to treat a variety of ailments including bruises, skin inflammation and musculoskeletal issues such as osteoarthritis, back pain, ankle sprains, knee joint injuries, joint distortion, myalgia and rheumatism. The biological activity of comfrey is proposed to be linked to natural anti-inflammatory compounds and other agents associated with skin repair and healing. Comfrey products are also used in cosmetic products. Topical comfrey preparations are widely available in Europe, USA and New Zealand, where they are unscheduled.

With reference to s 52E(c) of the Act, I note that the primary risk associated with comfrey is the presence of PAs which, through systemic exposure, can result in hepatotoxicity in humans. Short-term dermal use of comfrey poses a low risk of systemic exposure and hepatotoxicity due to poor dermal absorption of PAs. However, dermal preparations applied to broken skin, over large areas of the body, or for prolonged periods of time, will increase the risk of systemic absorption and the potential for subsequent liver damage. There is evidence that the risk to the user from exposures to less than 20% comfrey, including on unbroken skin, small areas and intermittent use, while low, is not negligible.[15] The EMA monograph limits the daily exposure to PAs via any given topical product to 1 microgram per day for adults and limits use to intact skin.[16] Currently available dermal preparations contain 5-20% comfrey dried root or leaf, but the PA levels in these preparations can vary considerably. Smaller, less mature leaves can have up to 16 times more PA than the large, mature leaves and roots contain considerably more PAs than leaves. I am therefore of the view that dermal preparations containing less than 20% comfrey still poses a risk that requires mitigation.

Finally, with regards to s 52E(d) of the Act, I note that Schedule 5 preparations of comfrey are required to contain the safety directions:

- Do not use on broken skin
- Do not use under occlusive dressing.

These simple label warnings clearly seek to mitigate the risk of systemic toxicity from PAs present in comfrey preparations (scheduling factors for Schedule 5 substances). If exempted, dermal preparations with low concentration of comfrey will not be required to carry such warning labels. Comfrey preparations are often marketed or used for indications including "to enhance wound healing" which involves application to broken skin. Such promoted use of topical comfrey in treating and repairing skin injuries further underscores the need for appropriate warning labels to prevent systemic absorption through incorrect usage of comfrey.

Considering the non-negligible risk of toxicity even at lower concentrations of comfrey, potential variability in PA contents in comfrey products and the continued requirement for warning statements to prevent inadvertent overexposure, I have decided to retain all dermal preparations of comfrey under Schedule 5 without any exception.

[15] Kimel et al, 2023, viewed 7 November 2024

[16] https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-monograph-symphytum-officinale-l-radix_en.pdf, viewed 7 November 2024

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