Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

13 July 2023

Confidentiality

All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

1. 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 the Health and Aged Care (the **Delegate**) under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[1] under subdivision 3D.2 of the Regulations in March 2023;
- 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 **8 August 2023**.

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

2. Interim decision on a proposed amendment referred to the Advisory Committee on Medicines Scheduling (ACMS #41, March 2023)

Interim decision in relation to celecoxib

Proposal

The applicant proposed the creation of a new Schedule 3 entry for celecoxib for oral use in capsules containing 200 mg or less per capsule when in packs containing not more than 10 dosage units. The new Schedule 3 entry would provide short-term treatment of period pain (primary dysmenorrhea) in adults and short-term treatment of acute pain in adults with muscle and joint injuries. The proposal also includes a new Appendix H entry for celecoxib to permit advertising of Schedule 3 preparations. Celecoxib is a non-steroidal anti-inflammatory (NSAID) medication currently captured in Schedule 4 of the Poisons Standard.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to celecoxib as follows:[2]

Schedule 4 – Amend Entry

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

Schedule 3 – New Entry

CELECOXIB in tablets or capsules of 200 mg or less, in a primary pack not containing more than 10 dosage units for the short-term treatment of acute pain due to primary dysmenorrhea or musculoskeletal or soft tissue injuries in adults.

Appendix H – New Entry

CELECOXIB

Index – Amend Entry

CELECOXIB

Schedule 4
Schedule 3
Appendix H

The Delegate's interim decision aligns with the applicant's proposal and the detailed reasons for the decision follow.

[2] 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 application to amend the current Poisons Standard with respect to celecoxib (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 41st meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Section 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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;
- Publications and references cited in the reasons below;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to s 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for celecoxib be amended in the Poisons Standard to include a Schedule 3 entry for short-term treatment in adults.

Members agreed that the relevant matters under section 52E(1) of the Act include: (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:

- Consistent with the broader NSAID/ COX-inhibitor class adverse events (cardiovascular events, hypertension, heart failure, renal toxicity etc), particularly among high-risk population groups, such as the elderly.
- Delay of diagnosis and risk of masking severe chronic conditions, such as endometriosis.
- Allergic reactions, attributable to the sulphonamide moiety, are possible but relatively uncommon.
- Risk of use in combination with other NSAIDs.
- Potential for misuse beyond indications.

Benefits:

- Relief of pain, some reduction in risk of upper gastrointestinal side effects relative to other agents.
- Patient benefit from NSAIDs can be variable so some may respond well to celecoxib.

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

- Short-term treatment of primary dysmenorrhea in adults and for the short-term treatment of acute pain in adults with musculoskeletal and/or soft tissue injury.

c) the toxicity of a substance

- Largely consistent with other NSAIDs; cardiovascular toxicity consistent with diclofenac.
- Acute toxicity reported at 400 mg daily dose, but most toxicity is related to chronic use.
- Higher toxicity risk in patients with renal disease and cardiovascular disease.

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

- Dose unit of 200 mg with 5 tablets would encourage short term use (maximum 5 days' supply).
- RASML would need to be considered in relation to pregnancy and allergy risks.
- Labelling should support short term use as well as avoiding use for other pain e.g. headache, osteoarthritis.
- Risk of chronic use should be avoided through smaller pack sizes to ensure patients seek review from their medical practitioner.

e) the potential for abuse of a substance

- Nil.

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

- Dysmenorrhea is complex, subject to significant rates of diagnostic error and/or delay and requires multimodal therapy and a high of personalisation.
- Slight benefit with regard to upper gastrointestinal safety relative to non-selective NSAIDs.
- Indications are captured as part of product registration process.
- Chronic use of OTC NSAIDs, despite guidance on short term use, is known to occur.

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 scheduling of celecoxib in the Poisons Standard to allow supply of celecoxib for short term use under the supervision of a pharmacist. The detailed

reasons for my decision follow.

I have considered all 6 public submissions. Of the 5 written public submissions received during the pre-meeting consultation period, 4 written responses received were fully supportive of the applicant's proposal and one was partially supportive. One response (without a written component) opposed the proposal, but my consideration of it is limited as no reasons for their opposition were provided.

Pursuant to s 52E(1)(a) of the Act, I acknowledge that celecoxib does not show significant clinical superiority compared to other NSAIDs for acute pain or dysmenorrhea management. However, as I will set out below, I am satisfied that the benefits of down-scheduling outweigh the risks because the safety of the substance with pharmacist intervention within the scope of my proposed Schedule 3 entry will ensure its appropriate use.

The risk factors for adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist. As a COX-2 selective NSAID, the risk profile includes a well-established risk of cardiovascular adverse events, particularly in those patients with renal disease and cardiovascular disease. Furthermore, adverse effects such as hypertension, heart failure and renal toxicity are comparable with other NSAIDs. Allergic reactions, attributable to the sulphonamide moiety contained within celecoxib, are also possible, however relatively rare.[3] Turning to paragraphs 52E(1)(a), (b) and (c) of the Act, I note that pharmacist supervision during supply would ensure appropriate identification of medication interactions, duplication of therapy with other NSAIDs and sulphonamide allergy.

My decision is in alignment with the applicant's proposed quantity of 10 dosage units of celecoxib 200 mg, which allows for a loading dose of 400 mg to be taken for acute pain. This is supported by the data submitted for the product registration of celecoxib as a prescription medicine,[4] whereby the loading dose for both musculoskeletal and/or soft tissue injury requires an initial dose of 400 mg, then 200 mg once or twice daily as required for up to 5 days. For primary dysmenorrhoea the approved dosage is 400 mg as a single dose or in divided doses on the first day, followed by 200 mg once a day on subsequent days. Patients may need to take an additional dose of 200 mg on any given day, if needed. Without a loading dose of 400 mg, a dose of 200 mg could potentially be sub-therapeutic and insufficient for most adults with acute pain conditions and would need to be demonstrated for a Schedule 3 product. Consistency with the data that has been relied upon for the TGA product registration process for the indications specified in the application is a factor in my decision pursuant to s 52E(1)(f) of the Act.

The pack size of 10 dosage units proposed is adequate to provide consumers over-the-counter access to celecoxib for short-term intervention for acute pain conditions for up to 5 days with a maximum daily dosage of 400 mg. I am of the view that this is sufficient for short-term treatment of musculoskeletal/soft tissue injury and primary dysmenorrhea and would discourage chronic use and reduce the risk of adverse events~~,~~ that is more likely to occur with prolonged use. The smaller pack size aimed at short-term use, will ensure patients seek review from their medical practitioner, if extended use past 5 days is required. This aligns with the Committee advice of 5 days' supply.

In alignment with the applicant's proposal, the scheduling entry in the decision provides a limitation on indications for use of celecoxib in the Schedule 3 context. I am satisfied that these indications are within the scope of limited acute pain conditions, that can be identified and overseen by a pharmacist.

[3] Giles A, Foushee J, Lantz E, Gumina G. Sulfonamide Allergies. Pharmacy (Basel). 2019 Sep 11;7(3):132. doi: 10.3390/pharmacy7030132. PMID: 31514363; PMCID: PMC6789825.

[4] Australian Product Information – Celebrex (Celecoxib) Capsules

I am of the view that restriction of access to adults 18 years and over, is consistent with the Therapeutic Guidelines recommendations,[5] product safety data and product information, which indicates celecoxib is not approved for use in patients under 18 years of age.

Concerning s 52E(1)(d) of the Act, advisory statements in the Required Advisory Statements for Medicine Labels (RASML) would be required to provide adequate warnings on labelling, to ensure short term usage, and warnings particularly relation to pregnancy and allergy risks.

The proposal for an Appendix H entry for celecoxib to permit advertising of Schedule 3 preparations is consistent with other NSAIDs that are advertised, provided adequate information is supplied in the Consumer Medicines Information (CMI) regarding potential adverse effects, allergy risk and pregnancy warning. I note that advertising could serve as a prompt for patients to seek advice from a pharmacist who will assess if the product is appropriate in their circumstance, especially in the context of suitability for use in primary dysmenorrhea, but not secondary dysmenorrhea (which requires referral to a doctor).

I also note the regulation of celecoxib internationally, whereby comparable countries such as the United States, Canada, United Kingdom, Ireland and New Zealand have not made celecoxib available without a prescription. Further comparative considerations with respect to my decision are studies that demonstrate celecoxib at prescription doses have a similar safety profile to other OTC anti-inflammatory drugs when used at prescription doses.

In alignment with the SPF factors for Schedule 3, celecoxib is substantially low risk with pharmacist intervention to ensure safe and appropriate use of the medicine. There is no evidence of dependence with use, celecoxib has a well-established safety profile which is comparable to other NSAIDs when used short-term for acute conditions. Pharmacist consultation during provision will ensure that consumers are not using celecoxib long term to mask symptoms or delay diagnosis of a serious condition.

After consideration and discussion of the information provided in the application, the public submissions, advice provided by the Committee and the SPF factors for Schedule 3, I have made an interim decision to create a new Schedule 3 entry for celecoxib for short-term treatment in adults.

Implementation date

1 February 2024

[5] Adult dosages of oral NSAIDs used for musculoskeletal conditions | Therapeutic Guidelines (tg.org.au)

3. Interim decision on a proposed amendment referred to the joint meeting of the Advisory Committee on Medicines Scheduling (ACMS) and Advisory Committee on Chemicals Scheduling (ACCS) (Joint ACMS-ACCS #33, March 2023)

Interim decision in relation to azelaic acid

Proposal

A Delegate proposed amendments to the Poisons Standard with respect to azelaic acid. The amendments were intended to address non-therapeutic use of the substance, as well as clarify the existing entries for azelaic acid in Schedules 2 and 4.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to azelaic acid as follows:[6]

Schedule 5 – New Entry

AZELAIC ACID **except** when included in Schedules 2 or 4.

Schedule 4 – Amend entry

AZELAIC ACID for therapeutic use **except**~~:~~

~~a)~~ when included in Schedule 2.~~; or~~

~~b) in preparations containing 1% or less of azelaic acid for non-human use~~

Schedule 2 – Amend entry

AZELAIC ACID in dermal preparations for human therapeutic use.

Appendix E – New entry

[6] 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.

Poison	Warning statement	Safety Direction
Azelaic acid	A, E1	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 – If in eyes, wash out immediately with water

Appendix F– New entry

Poison	Warning statement	Safety Direction
Azelaic acid	1, 4	1 - Avoid contact with eyes 4 - Avoid contact with skin.

Index – Amend entry

AZELAIC ACID
Cross reference: NONANEDIOIC ACID

Schedule 5
Schedule 4
Schedule 2
Appendix E, clause 3
Appendix F, clause 4

The Delegate recommends an implementation date of **1 October 2024**, to allow industry sufficient time to accommodate the changes.

The Delegate's interim decision differs from the applicant's proposal and the detailed reasons for the decision follow.

Materials considered

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

- The Australian Industrial Chemicals Introduction Scheme (AICIS) evaluation statement on azelaic acid.
- The delegate-initiated proposal to amend the current Poisons Standard with respect to azelaic acid (the **Proposal**);
- The 4 public submissions, with 2 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 33rd meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**);
- The Globally Harmonized System of Classification and Labelling of Chemicals (GHS Rev. 9, 2021);

- Section 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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;
- Publications cited in the reasons below;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to s 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that the Poisons Standard be amended in relation to azelaic acid as set out below:[7]

Schedule 5 – New Entry

AZELAIC ACID **except** when included in Schedules 2 or 4.

Schedule 4 – Amend entry

AZELAIC ACID for therapeutic use **except**~~:~~

~~a)~~ when included in Schedule 2; ~~or~~

~~b) in preparations containing 1% or less of azelaic acid for non-human use~~

Schedule 2 – Amend entry

AZELAIC ACID in dermal preparations for human use **except** in preparations for cosmetic use when containing no more than 10% azelaic acid.

Index – Amend entry

AZELAIC ACID
Cross reference: NONANEDIOIC ACID

Schedule 5
Schedule 4
Schedule 2

Members agreed that the relevant matters under section 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:

[7] 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.

- Moderate to severe skin to eye irritation has been reported with 15-20% azelaic acid.
- Moderate to severe skin irritation.

Benefits:

- Keratolytic, comedolytic, antibacterial, antioxidant effects.
- Effective treatment of mild-to-moderate acne and rosacea.

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

- Cosmetic use: Products containing derivatives, also used a buffer in fragrances. Potential for long-term use in anti-ageing creams.
- Therapeutic use: topical formulations indicated for rosacea and acne.
- Emerging veterinarian use of azelaic acid derivatives for seborrheic dermatitis in animals (registered international products) e.g. adelmidrol.
- Industrial uses: wide ranging possible uses, including in adhesives, lubricants, cleaning products, inks and toners.

c) the toxicity of a substance

- Low acute oral toxicity (LD50 > 5000 mg/kg), low acute dermal toxicity (LD50 > 2000 mg/kg).
- Moderate to severe skin and eye reactions have been reported with products containing 15-20% azelaic acid.
- Not a skin sensitiser. Does not result in reproductive or developmental toxicity, not expected to be carcinogenic.

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

- For therapeutic use: cream and gel products available for topical use.
- Despite the wide range of possible uses, limited information on current industrial/domestic use in Australia.

e) the potential for abuse of a substance

- Nil.

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

- Prohibition in Asian countries for cosmetic use (skin whitening agent).
- There are cosmetic products in the market containing a derivative of azelaic acid.
- Cosmetic use (mainly overseas): topical formulation indicated for rosacea, acne. Used as a buffer in fragrances. These products have the significant potential to be imported into Australia.

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.

My decision primarily focusses on the risks and benefits to the public in accordance with s 52E(1)(a) of the Act, having regard to the industrial, cosmetic and therapeutic purposes for which azelaic acid is used pursuant to s 52E(1)(b) of the Act. The three main considerations in reaching my interim decision are: 1) the range of legitimate industrial uses for azelaic acid and its derivatives, which are not appropriately accommodated under the current entries for the substance; 2) the uncertainty concerning the risks associated with cosmetic use of azelaic acid; and 3) the therapeutic value of azelaic acid at higher concentrations, including its derivatives, despite potential skin and eye irritation. The detailed reasons for my decision follow.

I have considered all 4 public submissions received during the pre-meeting consultation period. The 2 written responses received were fully supportive of the proposal. Of the submissions received without a written component, one was supportive and the other opposed to the proposal. The respondent who opposed the proposal did not provide reasons for their opposition. Overall, the submissions were generally in favour of the scheduling proposal.

Industrial use of azelaic acid

I note, pursuant to s 52E(1)(b) of the Act, that azelaic acid has a wide range of valid industrial uses including in adhesives, lubricants and cleaning products. I recognise that access to azelaic acid for these uses is currently limited by the Poisons Standard as the substance is included only as a Pharmacy Only (Schedule 2) and Prescription Only (Schedule 4) medicine except for preparations containing 1% or less. It is likely industrial users of this chemical were not aware of the restrictions associated with the current scheduling.

In considering the SPF and with reference to s 52E(1)(c) of the Act, I am of the view that the industrial use of azelaic acid aligns with the scheduling factors for Schedule 5. Azelaic acid has low acute oral and dermal toxicity, is not a skin sensitiser, is not genotoxic and is not expected to be carcinogenic or result in reproductive or developmental toxicity, consistent with factors 1[8] and 2[9] for Schedule 5 as having a low toxicity and health hazard. In this light, simple safety directions and first aid instructions on the label would enable legitimate use and manage the risks of skin and eye irritation to users.

As such, I am satisfied to create an entry for azelaic acid in Schedule 5 to accommodate industrial use.

Therapeutic uses of azelaic acid

Largely in line with the initial proposal, my interim decision is to retain all therapeutic uses in Schedule 4, with the sole exception for human dermal therapeutic uses in Schedule 2.

In considering the benefits of azelaic acid for therapeutic use pursuant to s 52E(1)(a) of the Act, I note the therapeutic claims associated with azelaic acid include effective treatment of mild to moderate acne and rosacea as well as having keratolytic, comedolytic, anti-bacterial and antioxidant effects in humans. There is also emerging veterinary use of azelaic acid derivatives for the treatment of seborrheic dermatitis in animals, although these products are not yet registered for use in Australia by the APVMA. Currently, the two therapeutic products listed on the TGA's ARTG and available for sale in Australia are between 15%-20% concentration and are captured by the current and proposed Schedule 2 (Pharmacy Only) entry for azelaic acid.

[8] SPF factor 1 for Schedule 5 - The substance is non-corrosive and has a low toxicity.

[9] SPF factor 2 for Schedule 5 – The substance has a low health hazard.

I note that several products available to Australian consumers containing azelaic acid are used to treat acne and rosacea and claim to reduce inflammation. While these products are purported to be cosmetics, there is real potential that the nature of the claims of the products make them therapeutic goods in law as per the definition in the Act.

I am of the view that in the absence of relevant health professional oversight, the claims made by these 'consumer' products and the known potential for azelaic acid to cause skin and eye irritation, raises unacceptable risks to consumers. Although transient and reversible, the potential remains for consumers to be delayed in obtaining appropriate care. Similar concerns were highlighted in the interim decision for another application seeking to amend the azelaic acid entries in the Poisons Standard. Dermal preparations for human therapeutic use should be accessible with the availability of pharmacists to discuss the potential skin and eye irritation with patients prior to use. Therefore, the therapeutic use of azelaic acid should continue to be captured in Schedules 2 and 4 to protect consumers from products that make higher level claims of a therapeutic nature.

I am also of the view that the use of azelaic acid and its derivatives in animal-related treatments should be under the direction of veterinarians and be captured under Schedule 4, given the emerging evidence of its use for the treatment of dermatological conditions such as pruritus and erythema[10] in animals. It is important to note that only Schedules 4, 5, 6, 7 and 8 of the Poisons Standard are applicable for veterinary medicines/chemicals and therefore the current Schedule 2 entry would have no utility for the non-human use of azelaic acid.

Cosmetic uses of azelaic acid

In relation to preparations for cosmetic use, I have formed the opinion that: (i) azelaic acid and its derivatives may cause adverse reactions in people e.g. skin and eye irritation; and (ii) there have been various international limitations or restrictions placed upon azelaic acid-containing cosmetics, as noted in the information provided in the proposed amendment and from the public submissions. For example, azelaic acid is prohibited from use in cosmetics by the ASEAN Cosmetic Directive,[11] and that in New Zealand azelaic acid preparations for dermal use are pharmacy only medicines. On the other hand, the 2012 US Cosmetic Ingredient Review panel's assessment of azelaic acid noted that concentrations up 0.3% for leave on products and up to 10% for rinse off products were in use and concluded that these uses and concentrations were safe. Health Canada in 2022, restricted azelaic acid and its salts to a maximum concentration of 14% due to known therapeutic properties and the risk of skin irritation above 14%. The chemical also satisfies the criteria for classification as a Category 2 skin irritant (H315) and Category 2 eye irritant (H319) according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).[12]

Given this variation in approaches to mitigate the risks associated with the use of azelaic acid in cosmetics and the value attributed to professional advice being required or available for the therapeutic uses of azelaic acid under Schedule 4 and Schedule 2 entries, respectively, I am of the opinion that cosmetic preparations should be subject to the labelling requirements of Schedule 5. Furthermore, I am not convinced that there is sufficient information to justify a concentration cut-off for azelaic acid. A concentration cut-off would have resulted in some

[10] Palmitoylethanolamide and Related ALIAmides for Small Animal Health: State of the Art https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9496254/

[11] https://aseancosmetics.org/uploads/UserFiles/File/TECHNICAL%20DOCUMENTS/oct2015/Annex%20II%20of%20ACD%20rev%20August%202015-1.pdf

[12] https://unece.org/sites/default/files/2021-09/GHS_Rev9E_0.pdf

azelaic acid containing cosmetic preparations being unscheduled, and therefore exempt from labelling under the Poisons Standard.

Derivatives

My interim decision is to not exclude derivatives of azelaic acid in Schedules 2, 4 and 5 as I originally proposed. The intent behind excluding derivatives in the proposed entries was to ensure that pharmacologically and toxicologically dissimilar compounds were not inadvertently captured on the basis of having a similar chemical structure to azelaic acid. However, I agree with the Committee's advice that the scheduling of derivatives was likely to be pertinent to therapeutic use of the substance rather than industrial use and that it would be imprudent to exclude them from scheduling. Moreover, there is insufficient information available to me at this time to exclude derivatives of azelaic acid from scheduling in general.

Therefore, I have decided not to exclude azelaic acid derivatives from the proposed amendments to Schedules 2, 4 and 5 of the Poisons Standard.

Other matters

I have decided not to implement the proposed 1% cut off from Schedule 2 and to remove the existing 1% cut-off in Schedule 4. The 1% cut-off was initially entered into the Poisons Standard following a discussion in October 2005 when the Schedule 4 entry was amended to accommodate preparations for the treatment of cats and dogs. There is no information available to me at this time to indicate that such preparations are currently available in the Australian market. Therefore, I have decided that *derma*l preparations for non-human therapeutic use should—like all other preparations for non-human therapeutic use—be captured by Schedule 4.

Implementation date

1 October 2024

4. Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #36, March 2023)

Interim decision in relation to bromoxynil

CONTENT WARNING

The information below contains information regarding self-poisoning that some people may find distressing. The Department of Health and Aged Care acknowledges the devastating effects associated with acts of self-harm on individuals, their families, friends and communities. If you or someone you know needs additional support, please contact any of the below crisis support helplines:

Adult

- Lifeline: 13 11 14
- Suicide Call Back Service: 1300 659 467
- Beyond Blue: 1800 512 348
- MensLine Australia: 1300 789 978

Youth

- Kids Helpline (5-25 years): 1800 551 800
- Headspace: 1800 650 890
- ReachOut

Proposal

The applicant proposed the creation of a new Schedule 7 entry for bromoxynil for preparations containing greater than 1% of bromoxynil. Under the proposal, preparations containing 1% or less of bromoxynil would continue to be captured by the existing Schedule 6 entry.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to bromoxynil as follows:[13]

Schedule 7 – New Entry

BROMOXYNIL **except** when included in Schedule 6.

[13] 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.

Schedule 6 – Amend Entry

BROMOXYNIL in preparations containing 1.5% or less of bromoxynil.

Index – Amend Entry

BROMOXYNIL

Schedule 7
Schedule 6

The Delegate's interim decision differs from the applicant's proposal and the detailed reasons for the decision follow.

Materials considered

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

- The application to amend the current Poisons Standard with respect to bromoxynil (the **Application)**;
- The 3 public submissions, with 2 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 36th meeting of the Advisory Committee on Chemicals Scheduling (the **Committee**);
- Section 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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;
- A systematic review on means restriction of poison and method-specific suicide rates;[14]
- Data from the National Coronial Information System (NCIS);
- Data from the New South Wales Poisons Information Centre (NSW PIC);
- Data from the APVMA Public Chemical Registration Information System (PubCRIS);
- The Commission Implementing Regulation (EU) 2020/1276, Official Journal of the European Union;
- Publications and references cited in the reasons below;
- The Scheduling Policy Framework 2018 (the **SPF**) , pursuant to s 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for bromoxynil be amended in the Poisons Standard to include a Schedule 7 entry in the manner set out in my interim decision.

[14] Lim JS, Buckley NA, Chitty KM, Moles RJ, Cairns R. Association Between Means Restriction of Poison and Method-Specific Suicide Rates: A Systematic Review. JAMA Health Forum. 2021;2(10):e213042. doi:10.1001/jamahealthforum.2021.3042

The Committee also recommended an implementation date of **1 June 2024**, to allow industry sufficient time to accommodate scheduling changes.

Members agreed that the relevant matters under section 52E(1) of the Act include: (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 reasons for the advice included:

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

Risks:

- Serious harm may occur from the ingestion of large doses (40 – 100 g of bromoxynil mixed with equal parts of MCPA), with a high fatality rate despite appropriate and timely expert medical advice. There is no specific antidote.
- NSW PIC data confirms peer review literature that bromoxynil in combination with MCPA has caused fatalities when large doses (>40 g) has been consumed.

Benefits:

- The benefit includes control of 28 species (Bayer data) of broad-leaf weeds in a large range of crops, pastures and turf and forms part of the strategy to prevent weed-resistance, and thus has economic and societal value (e.g. food), and for environmental management of invasive weed, fire hazard reduction etc.

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

- Herbicide in domestic (for broad-leaf weeds, particularly useful in Buffalo lawns) and industrial (for broad-leaf weeds in crops, pasture and turf; and for environmental management of invasive weeds) settings.

c) the toxicity of a substance

- Developmental adverse effects (EU classify as Cat 1B for reproduction toxicity) with some concern over endocrine effects (thyroid toxicity in Fischer F344 rats).
- Developmental toxicity has been observed in animals, but PPE and other safeguards reduce the risk – with acceptable MoE (EU modelling).
- European Chemicals Agency (ECHA) states: is fatal if inhaled, is toxic if swallowed, is very toxic to aquatic life with long lasting effects, is suspected of damaging the unborn child, may cause an allergic reaction.
- Suspected reproductive toxicity.
- Suspected to be skin sensitising.

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

- A variety of concentrations and presentations in APVMA registered products (max. concentration around 200 g/L).

- Concentrated formulations available to domestic users (smaller volumes ≤ 500 mL) and commercial users (larger volumes).
- Dilute formulations available for domestic users (0.6% - 1.2% hose-on formulations and packaging).
- If in Schedule 7, herbicides containing concentrated bromoxynil formulations will still be available to industry/agriculturalists.

e) the potential for abuse of a substance

- Increasing rate of deliberate self-poisoning, particularly by consumers in a domestic setting.

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

- Strong evidence that means restriction of poison is associated with reductions in method-specific suicide rates without an equivalent shift towards other methods.
- Consideration should be given to eliminating pesticides with human fatality rates above 5%.
- Increasing prohibition in USA, Canada and EU, moving away from bromoxynil for domestic use.
- Animal poisons centre data suggests dramatic increase of poisons over the past 3 years in domestic animals.
- Other potential controls that could be implemented, such as stenching agents to deter misuse.

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 current Poisons Standard in relation to bromoxynil. This follows consideration of various data indicating an increased incidence of intentional ingestion of products containing high concentrations of bromoxynil, resulting in significant adverse effects in humans including death. I am of the view that the risks to human health and safety of these products to the general public outweigh their benefits. In coming to my decision, I have relied predominantly on paragraphs (a), (b), (c) and (d) of section 52E(1) of the Act. I have provided detailed reasons for my decision below.

I have considered the information provided in the original application, and the 2 written public submissions received during the pre-meeting consultation period. The latter were fully supportive of the applicant's proposal. 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. One response without a written component was received that was opposed to the proposal. This respondent did not provide reasons for their support or opposition.

Bromoxynil is a nitrile herbicide, that disrupts energy production and respiration in plants via uncoupling oxidative phosphorylation in mitochondria. Similarly, bromoxynil can uncouple and or inhibit oxidative phosphorylation in animals, including humans.

The available information indicates that the occurrence of intentional ingestion of products containing bromoxynil frequently involves highly concentrated products, resulting in serious harm and outcomes, despite subsequent expert medical intervention and care. To date, there is no specific antidote available for use in bromoxynil poisonings. Data obtained from the New South Wales Poisons Information Centre (NSW PIC) and the National Coronial Information System (NCIS) have highlighted that such intentional ingestion has resulted in a number of fatalities, in particular in urban or domestic settings.

I note the main benefit of bromoxynil is its control of various broad-leaf weeds when used either alone or in combination with other herbicides, e.g. MCPA (2-methyl-4-chlorophenoxyacetic acid) and diflufenican. High concentration formulations are particularly useful in commercial and agricultural settings involving large land areas as they are more cost effective and transportable than dilute formulations. In these types of settings, bromoxynil protects various crops, pastures, and turf from competing weeds and is also used for the environmental management of invasive weeds. While higher concentrations are accessible and marketed for home garden use, the land area for this type of application is considerably smaller and therefore the cost and transport benefits of these preparations compared to dilute preparations are less significant. Dilute products also provide the unique benefit of having the product ready for use in a domestic setting, thereby minimising the need to decant, mix and dilute the preparation before application.

Considering the risks of these dilute preparations, I concur with the Committee that numerous dilute products are packaged as 'hose-on' formulations that encourage their appropriate use and serve to minimise accidental or deliberate exposure to the substance. While the harm to people intentionally ingesting *dilute* preparations of bromoxynil is still a possibility, dilute formulations require the consumption of larger volumes compared with concentrated products and may therefore reduce the incidence of fatal outcomes in the general, domestic population. This would be consistent with similar harm minimisation strategies, including evidence that indicates restricting access to poisonous substances is related to decreases in method-specific suicide rates and does not result in an equivalent shift to other methods.[15]

In considering the SPF, I am of the view that high concentration products align more consistently with Schedule 7 factors, namely a high health hazard and a high potential for causing harm at low exposure, whereas dilute products remain consistent with the factors of Schedule 6. Furthermore, placing higher concentrated formulations of bromoxynil in Schedule 7 and therefore limiting their access to commercial and agricultural users, would be consistent with the scheduling of such formulations and provide an appropriate balance of the risks and benefits to users.

Most of the 164 bromoxynil products registered containing more than 1.5% bromoxynil are available in large quantities and not marketed to the domestic user.[16] Moreover, products with concentrations less than 1.5% of bromoxynil would still be available to the general public under these proposed amendments to the scheduling of bromoxynil in the Poisons Standard. Considering the smaller land areas required to be maintained by the typical domestic user, I am satisfied that dilute formulations of bromoxynil will be sufficient for the purposes of domestic use. In addition, I note that there are several broad leaf herbicide alternatives available for use in the domestic market. I am of the opinion that this amendment will have a minimal impact on domestic users, for whom dilute and alternative preparations will still be available under Schedule 6.

[15] JAMA Health Forum – Health Policy, Health Care Reform, Health Affairs | JAMA Health Forum | JAMA Network

[16] Public Chemical Registration Information System Search - portal.apvma.gov.au

I agree with the Committee that an extended implementation period is warranted to allow: (i) the agricultural chemical industries to make the necessary adjustments to product labelling and supply; and (ii) the applicable State and Territory entities to make the necessary adjustments to their compliance regimes for Schedule 7 substances, where appropriate.

Implementation date

1 June 2024

Interim decision in relation to dioxane

Proposal

A Delegate proposed the deletion of the Appendix G entry for dioxane. The Appendix G entry currently exempts from scheduling controls any preparation containing 100 mg/kg or less of dioxane. Deletion of the Appendix G entry would reduce this exemption limit to the default of 10 mg/kg for Schedule 6 substances, placing all preparations containing greater than this concentration of dioxane in Schedule 6.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to dioxane as follows:[17]

Schedule 6 – Amend Entry

DIOXANE **except**:

a) in preparations for cosmetic or human internal therapeutic use containing less than 0.001% of dioxane; or

b) in other preparations containing less than 0.01% of dioxane.

Appendix G – Delete Entry

POISON	CONCENTRATION (QUANTITY PER LITRE OR KILOGRAM)
~~DIOXANE~~	~~100 mg~~

Index – Amend Entry

DIOXANE

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

Please note that there are no amendments to the entries for dioxane in Appendix E or Appendix F.

The Delegate's interim decision differs from the proposal in that suitable amendments will be made to the existing Schedule 6 entry for the substance such that the 100 mg/kg limit will remain in place for all preparations except those for cosmetic or human therapeutic use, which will revert to the default limit of 10 mg/kg for Schedule 6 poisons. The detailed reasons for the decision follow.

Materials considered

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

[17] 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.

- The proposal to amend the current Poisons Standard with respect to dioxane;
- The 6 public submissions, with 4 including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 36th meeting of the Advisory Committee on Chemicals Scheduling (the **Committee**);
- The evaluation statement on dioxane published by Australian Industrial Chemicals Introduction Scheme (AICIS) in June 2022;
- The Globally Harmonized System of Classification and Labelling of Chemicals (GHS Rev. 9, 2021);
- The International Council for Harmonisation (ICH) of technical requirements for pharmaceuticals for human use, Impurities: Guideline for residual solvents Q3C(R8);
- The Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2023;
- The Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products;
- Section 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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;
- Publications cited in the reasons below;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to s 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that the Poisons Standard be amended in relation to dioxane as follows:[18]

Appendix G – Delete Entry

POISON	CONCENTRATION (QUANTITY PER LITRE OR KILOGRAM)
~~DIOXANE~~	~~100 mg~~

The Committee did not recommend any amendments to the Schedule 6, Appendix E or Appendix F entries for dioxane.

The Committee also recommended an implementation date of **1 June 2024**, to allow industry sufficient time to accommodate the new limit.

Members agreed that the relevant matters under section 52E(1) of the Act include: (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.

[18] 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.

The reasons for the advice included:

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

Risks:

- Carcinogenic potential for humans based on animal studies.

Benefits:

- Many industrial and household products, such as cosmetics and detergents, contain dioxane as an impurity.

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

- Used as a solvent in several industrial and commercial products such as inks, adhesives and dyes.

c) the toxicity of a substance

- Animal studies confirm potential for hepatocellular adenoma/carcinomas. Nasal squamous cell carcinomas, rare olfactory neuroblastoma and adenocarcinomas.
- GHS Category 1B carcinogen – animal studies demonstrate benign and malignant tumours were found at multiple sites. Group 2B carcinogen in IARC monographs.
- Readily absorbed through oral and inhalation routes, and to a limited extent via the transdermal route.

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

- Range as an impurity from <10 mg/kg in cosmetics up to 200 mg/kg in consumer products such as shampoo and body wash.

e) the potential for abuse of a substance

- Nil.

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

- Pharmaceuticals may contain up to 380 mg/kg as a residual solvent under the ICH Q3C (R5) guidelines.
- More information needs to be sought regarding the levels of dioxane present in Australian products.
- Main exposure concern is still as an impurity in cosmetic and consumer products that contain ethoxylated chemicals.

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 current Poisons Standard in relation to dioxane. The detailed reasons for my decision follow.

Dioxane (also known as 1,4-dioxane) is a heterocyclic organic compound that has a number of industrial uses. The primary human health concern is its presence as an impurity or contaminant in the manufacture of ethoxylate surfactants, which are used in a wide range of

cosmetic and domestic products. These include shampoos, conditioners, shower gels, skin moisturisers, air fresheners, paints, inks, foams, dyes and adhesives.

The existing Appendix G entry for dioxane exempts these products from the Schedule 6 classification in the Poisons Standard when the level of dioxane does not exceed 100 mg/kg. The evaluation of dioxane by AICIS (June 2022) indicated that the toxicity profile of dioxane remains consistent with the Schedule 6 factors in the SPF. Furthermore, the evaluation recommended an amendment to the Appendix G entry to reduce the minimum level of dioxane from 100 mg/kg to 10 mg/kg at which scheduling controls would apply. The AICIS recommendation cited advances in manufacturing practices and an increased body of evidence of the potentially hazardous effects of dioxane exposure on humans as the basis for the proposed amendment to the Poisons Standard.

In reference to paragraphs 52E(1)(a) and (c) of the Act, I agree with the Committee's concerns regarding the carcinogenic potential of dioxane, and the risks associated with repeat and unprotected exposure. Dioxane is classed as a Category 1B carcinogen under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), with considerable evidence of carcinogenicity in animal studies and a Group B carcinogen (a possible human carcinogen) by the IARC.

Based on these factors, I agree with both the AICIS assessment and the advice of the Committee that dioxane warrants entry in Schedule 6 of the Poisons Standard. Moreover, the reduction of human exposure to dioxane is desirable wherever it is possible to do so, while taking into consideration the nature of the product and the associated expected extent of exposure.

The Appendix G entry for dioxane was established by the National Drugs and Poisons Scheduling Committee (NDPSC) in 1998. The existing limit of 100 mg/kg was considered a toxicologically acceptable level and the presence of the substance below this limit in consumer products was not expected to pose a significant health risk to the public. However, I recognise that in the time since this decision was made there has been a significant body of research performed on the effects of dioxane on human health, and a considerable international effort to reduce the levels of this substance in goods.

With regards to pharmaceuticals, the International Council for Harmonisation (ICH) has established guidelines for the presence of solvent residues in pharmaceuticals for human use[19], including a limit on dioxane of 380 mg/kg due to its inherent toxicity. However, the TGA's Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2023[20] (the **PID**) includes a limit of 10 mg/kg (or "below the level of detection") on dioxane content when present as an impurity for many ethoxylated solvents.[21] The significantly tighter restriction in the PID indicates the reduction in dioxane content in preparations for human therapeutic use is recognised as both desirable and achievable. I note that dioxane is only reported as an ingredient in one product on the Australian Register of Therapeutic Goods (ARTG), and therefore I expect there would be minimal impact from the loss of the Appendix G limit for dioxane as it applies to internal therapeutic preparations for human use.

While dioxane is a prohibited substance in cosmetic products in the EU (Cosmetics Regulation No 1223/2009), the European Scientific Committee on Consumer Safety concluded in 2015 that a trace level of 10 mg/kg of dioxane in cosmetic products was considered safe. The public submissions, notably including those from representatives of the cosmetics industry, were supportive of this trace level. Concordant with the Committee's recommendation, I consider that the removal of the Appendix G entry for dioxane resulting in the default limit of 10 mg/kg (0.001%) under the Poisons Standard, would be appropriate for cosmetics.

[19] ICH_Q3C-R8_Guideline_Step4_2021_0422.pdf

[20] Therapeutic Goods (Permissible Ingredients) Determination (No. 3) 2023 (legislation.gov.au)

[21] These include C12-13 Pareth-23, C12-13 Pareth-3, Ceteareth-33, Octyldodeceth-25, Oleth-2, PEG-4 Laurate and PEG-40 Sorbitan Diisostearate

With s 52E(1)(d) in mind, I note that the dermal absorption of dioxane has been demonstrated to be limited (0.3% for skin not under occlusion)[22] when compared to the oral and inhalational routes. Therefore, the potential for human exposure to dioxane from rinse-off preparations such as shampoos, shower gels and detergents, and the likelihood of exposure to dioxane from other products such as paints, dyes and inks, is suitably low such that there is insufficient risk of harm to human health if a limit of 100 mg/kg (0.01%) were to remain for dioxane in these products. Consistent with the information provided in the public submissions, I am of the opinion that exposure to dioxane from these products, would be restricted by their normal use and therefore I remain of the view that the existing limit of 100 mg/kg (0.01%) under which dioxane is not scheduled is appropriate for these products.

To give effect to the different limits at which certain dioxane preparations are or are not scheduled under the Poisons Standard, I have decided to remove the Appendix G entry for dioxane from the Poisons Standard and instead specify the limits within the existing Schedule 6 entry for dioxane. The 100 mg/kg (0.01%) limit will remain in place for all preparations except those for cosmetic or human therapeutic use, which will revert to the default limit for all Schedule 6 poisons of 10 mg/kg (0.001%).

I agree with the Committee that an extended implementation period is warranted to allow relevant industries to make the necessary adjustments to product labelling and supply streams.

Implementation date

1 June 2024

[22] ECETOC, 1983 https://www.ecetoc.org/wp-content/uploads/2021/10/JACC-002.pdf

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