Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

4 September 2023

Contents

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

This web publication constitutes a notice for the purposes of regulation 42ZCZS and regulation 42ZCZX of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulations 42ZCZS and 42ZCZX, this notice publishes:

- the decisions made by a delegate[1] of the Secretary of the Department of Health and Aged Care (the **Delegate**) pursuant to regulations 42ZCZR and 42ZCZU
- the reasons for those final decisions, and
- the date of effect of those decisions.

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 defined for individual decisions.

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

2 Final decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #41, March 2023)

2.1 Final 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 **Proposal**). 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 included 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.

Final decision

Pursuant to regulation 42ZCZR of the Regulations, the Delegate has made a final decision to confirm the interim decision and 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

[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 final 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**).[3]
- The 2 public submissions received in response to the interim decision consultation under regulation 42ZCZP of the Regulations (the **Submissions**).
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.
- Publications and references cited in the reasons below.
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

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

I have made a final decision to confirm my interim decision to amend the current Poisons Standard with respect to celecoxib. My reasons for making the final decision are those set out in the interim decision. In making my final decision, I have taken into account the material detailed in the interim decision and the Submissions, the majority of which for both consultation periods were in support of the interim decision.

I have noted that two public submissions were received before the second closing date in response to the call for further submissions published on 13 July 2023 under regulation 42ZCZP of the Regulations. Both submissions were in full support of the interim decision and included a written component.

Creation of 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 am of the view that the creation of a Schedule 3 entry for celecoxib provides benefit to the public through increased access for short term use under the supervision of a pharmacist. In terms of safety, celecoxib has a well-established safety profile comparable to other NSAIDs and any risk factors such as adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist.

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

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.

Implementation date

1 February 2024

3 Final decisions on proposed amendments referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #33, March 2023)

3.1 Final 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.

Final decision

Pursuant to regulation 42ZCZR of the Regulations, the Delegate has made a final decision to confirm the interim decision and amend the current Poisons Standard in relation to azelaic acid as follows:[4]

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

Item	Poison	Statement code	First aid instructions
31a	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

[4] 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.

Appendix F – New entry

Item	Poison	Statement code for safety directions	Safety Direction
32a	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

Materials considered

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

- The delegate-initiated proposal to amend the current Poisons Standard with respect to azelaic acid (the **Proposal**).
- The 4 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions).**
- The Australian Industrial Chemicals Introduction Scheme (AICIS) evaluation statement on azelaic acid.
- The Globally Harmonized System of Classification and Labelling of Chemicals (GHS Rev. 9, 2021).
- The advice received from the 33rd meeting of the Advisory Committees on Medicines and Chemical Scheduling in joint session (the **Committee**).[5]
- The 4 public submissions received in response to the interim decision consultation under regulation 42ZCZP of the Regulations (the **Submissions**)
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

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

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

I have made a final decision to confirm my interim decision to amend the current Poisons Standard with respect to azelaic acid. My reasons for making the final decision are those set out in the interim decision. In making my final decision, I have considered the material detailed in the interim decision and the Submissions, which were all in support of the interim decision.

I note that in their public submission through the consultation, the interim decision was supported by the Australasian College of Dermatologists (ACD) who provided comment that the risk of skin irritation when used in cosmetic preparations, usually at a concentration of 10% or less, would be minimal. The ACD advised that they supported all cosmetic use of azelaic acid being captured by the new Schedule 5 entry.

In confirming my interim decision, I have taken into consideration the 4 public submissions that were all in support of the interim decision for azelaic acid and have provided an implementation date of 1 October 2024 to allow time for industry to make any required amendments following the change.

Implementation date

1 October 2024

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

4.1 Final 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 (the **Proposal**). Under the Proposal, preparations containing 1% or less of bromoxynil would continue to be captured by the existing Schedule 6 entry.

Final decision

Pursuant to regulation 42ZCZR of the Regulations, the Delegate has made a final decision to confirm the interim decision and amend the current Poisons Standard in relation to bromoxynil as follows:[6]

Schedule 7 – New Entry

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

Schedule 6 – Amend Entry

BROMOXYNIL in preparations containing 1.5% or less of bromoxynil.

[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.

Index – Amend Entry

BROMOXYNIL

Schedule 7
Schedule 6

Materials considered

In making this final 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 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 Chemical Scheduling (the **Committee**).[7]
- The public submission received in response to the interim decision consultation under regulation 42ZCZP of the Regulations (the **Submissions**).
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.
- A systematic review on means restriction of poison and method-specific suicide rates.[8]
- 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.
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

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

I have made a final decision to confirm my interim decision to amend the current Poisons Standard with respect to bromoxynil. My reasons for making the final decision are those set out in the interim decision.

In making my final decision, I have taken into account the material detailed in the interim decision. I have noted that the single public submission was received before the second closing date in response

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

[8] 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

to the call for further submissions published on 13 July 2023 under regulation 42ZCZP of the Regulations, was supportive of the interim decision.

In confirming my interim decision, I have provided an extended implementation period 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

4.2 Final decision in relation to dioxane

Proposal

A Delegate proposed the deletion of the Appendix G entry for dioxane (the **Proposal**). 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.

Final decision

Pursuant to regulation 42ZCZR of the Regulations, the Delegate has made a final decision to vary the interim decision and amend the current Poisons Standard in relation to dioxane as follows:[9]

Schedule 6 – Amend Entry

DIOXANE **except**:

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

b) in other preparations containing 0.01% or less 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

[9] 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.

Appendix F, Part 3
~~Appendix G~~

Materials considered

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

- The proposal to amend the current Poisons Standard with respect to dioxane (the **Proposal**).
- The 6 public submissions 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 Chemical Scheduling (the **Committee**).[10]
- 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.
- The 3 public submissions received in response to the interim decision consultation under regulation 42ZCZP of the Regulations (the **Submissions**).
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

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

I have made a final decision to vary my interim decision to amend the current Poisons Standard with respect to dioxane. My reasons for making the final decision are those set out in the interim decision. In making my final decision, I have taken into account the material detailed in the interim decision and the 3 public submissions received before the second closing date in response to the call for further submissions published on 13 July 2023 under regulation 42ZCZP of the Regulations.

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

I acknowledge the point raised in the submission from Accord Australia regarding the convention for exemption limits in the Poisons Standard. I have therefore decided to make a minor amendment to the proposed Schedule 6 Poison Standard entry and vary the interim decision such that relevant preparations containing dioxane at or below the limits specified in the Schedule 6 entry are exempt from controls under the Poisons Standard. The other 2 submissions received in relation to dioxane were in support of the interim decision published on 13 July 2023.

I have provided an implementation date of 1 June 2024 to allow industry sufficient time to accommodate the new limit.

Implementation date

1 June 2024

5 Final decisions on proposed amendments to the current Poisons Standard under regulation 42ZCZU

In my capacity as a Delegate of the Secretary for the purpose of regulation 42ZCZU of the Regulations, I have made final decisions under regulation 42ZCZU with respect to the following substances:

- salbutamol
- nitazenes
- velagliflozin, and
- vadadustat.

5.1 Final decision in relation to salbutamol

Final Decision

Pursuant to regulation 42ZCZU of the Regulations, a Delegate of the Secretary has made a final decision to amend the current Poisons Standard in relation to salbutamol as follows:[11]

Schedule 3 - Amend Entry

SALBUTAMOL as the only therapeutically active substance:

a) in metered aerosols delivering 100 micrograms or less of salbutamol per metered dose; or

b) in dry powders for inhalation delivering 200 micrograms or less of salbutamol per dose~~; and~~

~~where supply is limited:~~

~~c) for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma and other stimuli known to induce bronchospasm; or~~

~~d) for the treatment of a person with a record of previous supply from a pharmacy; or~~

~~e) to persons authorised under a law of a State or Territory to use or supply salbutamol in the practice of their profession; or~~

~~f) for use in institutional first aid; and~~
~~where paragraph (c) or (d) applies—supply is limited to one primary pack of salbutamol per person being treated~~.

[11] 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 final decision, the Delegate considered the following material:

- Subsection 52E(1) of *the Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (f) any other matters considered necessary to protect public health.
- Information regarding the current status of salbutamol supplies in Australia.[12]
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

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

In determining that this matter will be a delegate-only decision I have taken into account the current status of salbutamol supplies[13] and consumer purchasing behaviour. I note there are no current or projected shortages of salbutamol and consumer purchasing behaviour appears to have stabilised since Australia has transitioned into the new normal following the rise of COVID-19. In particular I note that:

- The amendment will remove additional restrictions that were placed on salbutamol in March 2020, in response to potential supply shortages due to panic-buying and stockpiling in association with COVID-19. The additional restrictions were added to protect public health by ensuring continued access for all patients with a legitimate clinical need.
- In relation to 52E(1)(a) and (b) of the Act, there have been no reports of current or anticipated shortages of salbutamol metered dose aerosol or dry powder for inhalation products. The reported stock levels suggest treatment for patients with chronic lung conditions are no longer at risk of being interrupted. As such I recognise the level of community demand, in particular the intent of stockpiling, appears to have normalised.
- Since supplies of salbutamol are not currently at risk and consumer purchasing behaviour appear to have normalised, I acknowledge pharmacists can use their professional discretion to determine when supply of salbutamol is appropriate, whilst maintaining the regulatory controls that apply to Schedule 3 medicines with regards to access.
- I have considered the matters under part (f) of section 52E of the Therapeutic Goods Act 1989 to be relevant to this decision. The additional controls that were placed on salbutamol in consideration of the rise of COVID-19 are no longer required to protect public health, as supply shortages have now abated. Patients who require salbutamol to treat symptoms of asthma and COPD are no longer at risk of supply interruptions.

On the basis of the above considerations, I have decided to amend the current Poisons Standard in the manner set out above. This matter was not referred to an expert advisory committee.

Implementation date

1 October 2023

[12] Therapeutic Goods Administration, Medicine shortage, reports database: https://apps.tga.gov.au/prod/MSI/search/
[13] Therapeutic Goods Administration, Medicine shortage, reports database: https://apps.tga.gov.au/prod/MSI/search/

5.2 Final decision in relation to nitazenes

Final Decision

Pursuant to regulation 42ZCZU of the Regulations, a Delegate of the Secretary has made a final decision to amend the current Poisons Standard in relation to nitazenes as follows:

Schedule 9 – New entries

BUTONITAZENE

ETODESNITAZENE

ETONITAZEPIPNE

ETONITAZEPYNE

FLUNITAZENE

ISOTONITAZENE

METODESNITAZENE

METONITAZENE

PROTONITAZENE

Index – New entries

BUTONITAZENE
cross reference: CAS No. 95810-54-1

Schedule 9

ETODESNITAZENE
cross reference: CAS No. 14030-76-3, ETAZENE

Schedule 9

ETONITAZEPIPNE
cross reference: CAS No. 734496-28-7, N-PIPERIDINO ETONITAZENE

Schedule 9

ETONITAZEPYNE
cross reference: CAS No. 2785346-75-8, N-PYRROLIDINO ETONITAZENE

Schedule 9

FLUNITAZENE
cross reference: CAS No. 2728-91-8

Schedule 9

ISOTONITAZENE
cross reference: CAS No. 14188-81-9

Schedule 9

METODESNITAZENE
cross reference: CAS No. 14030-77-4, METAZENE

Schedule 9

METONITAZENE
cross reference: CAS No. 14680-51-4

Schedule 9

PROTONITAZENE
cross reference: CAS No. 95958-84-2

Schedule 9

Materials considered

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

- Subsection 52E(1) of *the Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.
- Alerts published by the Departments of Health in Victoria,[14] New South Wales[15],[16] and the Australian Capital Territory.[17]
- The advice provided by the United Kingdom's Advisory Council on the Misuse of Drugs (ACMD) regarding 2-benzyl benzimidazole and piperidine benzimidazolone opioids.[18]
- The United States' Drug Enforcement Administration's (DEA) dossier on benzimidazole-opioids (nitazenes).[19]
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- The Handbook.

[14] Vic Dept of Health drug alert https://www.health.vic.gov.au/drug-alerts/yellow-powder-containing-protonitazene-may-be-sold-as-ketamine
[15] NSW Health warning https://www.health.nsw.gov.au/news/Pages/20221222_01.aspx
[16] NSW Health warning https://www.health.nsw.gov.au/news/Pages/20230505_02.aspx
[17] ACT Health alert https://www.health.act.gov.au/public-health-alert/public-health-alert-dangerous-drug-warning-canberrans
[18] ACMD advice on benzimidazolone opioids https://www.gov.uk/government/publications/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids/acmd-advice-on-2-benzyl-benzimidazole-and-piperidine-benzimidazolone-opioids-accessible-version
[19] DEA dossier on nitazenes https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf

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

In exercising my power under paragraph 52D(2)(a) of the Act, I have taken into account the information provided in the materials listed above, and the matters specified under s 52E of the Act and the SPF. In particular, I note:

- Regarding s 52E(1)(b) of the Act, I recognise that while the nitazene family of substances were originally developed with the intention to be used in anaesthesia, the pronounced potency of the substances and associated risk of respiratory depression and death means that they are considered unsuitable for use in a therapeutic context. I also recognise that there are increasing reports of the presence of these substances in drugs intended for recreational use, which has resulted in a proportionate increase in adverse events and fatalities associated with exposure to nitazenes. While these reports are largely limited to overseas jurisdictions thus far, I note with concern the recent reports of the detection of nitazenes in seizures of heroin and other illicit and counterfeit drugs in Australia.
- In relation to s 52E(1)(c) of the Act, I note that substances in the nitazenes class are potent agonists of the opioid receptors and have been estimated in some instances to be hundreds of times more potent than morphine.[20] The effects of nitazenes are similar to other opioids and include analgesia and euphoria. However, the elevated potency of the substances presents a high risk of adverse effects including respiratory depression which can lead to death. Of particular concern is that the typical therapeutic dose of an opioid antagonist such as naloxone, which acts as a life-saving antidote in an instance of opioid overdose, may not be as effective in the case of nitazene exposure due to the potency of these substances.[21]
- In relation to the benefits and risks of the use of the substances pursuant to s 52E(1)(a) of the Act, I note that public exposure appears to be entirely recreational—there being no established therapeutic value for the substances—and their abuse and illicit use poses a significant risk to public health. This aligns with the factor for an entry in Schedule 9 of the Poisons Standard that 'the substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use'. Moreover, I am satisfied that the risks are of such significance as to warrant limiting access to these substances for strictly controlled medical and scientific research.
- With regards to s 52E(1)(d) of the Act, in considering material from the ACMD and DEA, I note that the majority of cases of detection of nitazenes internationally have been as contaminants and/or adulterants in seizures of illicit drugs such as heroin. However, the novel nature of these substances means that in many international jurisdictions nitazenes are not regulated as a class of substances, and many individual substances within the class do not have controls on their manufacture, supply or use. In Australia, only clonitazene and etonitazene (both Schedule 9) are presently included in the Poisons Standard.
- In consideration of s 52E(1)(e) of the Act, I note from numerous sources, including the considered materials, nitazenes presents a high potential for abuse. This is expected for opioid substances with such potent activity.
- Finally, regarding s 52E(1)(f) of the Act, I have noted that as of 3 February 2023, 10 synthetic opioids have been recommended to be made Class A substances in the United Kingdom, including the 9 substances specified in this decision. The Class A classification recognises the

[20] Vandeputte et al https://link.springer.com/article/10.1007/s00204-022-03276-4
[21] https://adf.org.au/drug-facts/nitazenes/

potential harm to public health associated with these substances and is equivalent to Schedule 9 in the Poisons Standard.

On the basis of the above considerations and the information included in the considered materials, I have decided to amend the Poisons Standard in the manner laid out above. Due to the clear and immediate public health risks associated with these substances, and there being no current legitimate use of the substances that would be restricted by their inclusion in Schedule 9, this amendment was not formally referred to an expert advisory committee for their advice.

Implementation date

1 October 2023

5.3 Final decision in relation to velagliflozin

Final Decision

Pursuant to regulation 42ZCZU of the Regulations, a Delegate of the Secretary has made a final decision to amend the current Poisons Standard in relation to velagliflozin as follows:[22]

Schedule 4 – New Entry

VELAGLIFLOZIN

Index – New Entry

VELAGLIFLOZIN

Schedule 4

Materials considered

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

- The application to amend the current Poisons Standard with respect to velagliflozin (the **Application**).
- 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.
- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- the Handbook.

[22] 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.

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

In determining that this matter will be a delegate-only decision I have taken into account the information provided in the Application from the applicant, the Australian Pesticides and Veterinary Medicine Authority (APVMA), and the matters outlined under s 52E of the Act and the SPF. In particular I note that:

- In relation to s 52E(1)(a) of the Act, the proposed amendment to the Poisons Standard is to include an entry for velagliflozin in Schedule 4 based upon its benefit to the treatment of diabetes in companion animals. The Application did not request or provide information in support of a concentration cut-off for the substance to be unscheduled. The substance currently has no established therapeutic value in humans and I note that velagliflozin is not registered for human use either in Australia or internationally.
- Regarding s 52E(1)(b) of the Act, the intended use of the substance is treatment of diabetes in cats. Velagliflozin belongs to the sodium dependent glucose co-transporter (SGLT) inhibitor class of drugs. The substance decreases blood glucose and insulin concentrations through selectively binding the SGLT2 receptor. The intended product formulation will contain 15 mg/mL of velagliflozin as the technical grade active constituent (TGAC) in a liquid solution. It is intended to be a prescription medicine for oral administration by veterinary professionals and cat owners as a home veterinary product. Consistent with the factors for inclusion in Schedule 4, products containing velagliflozin require veterinary diagnosis and monitoring to ensure appropriate and safe use.
- In relation to s 52E(1)(c) of the Act, the APVMA provided a Human Health Risk Assessment (HHRA) for the TGAC and the intended product formulation containing velagliflozin at 15 mg/mL. The findings from the HHRA concluded that the risks to human health and safety posed by this substance were acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act 1994*.
- In review of the HHRA, the levels for acute oral toxicity were low in studies conducted in both mice (LD_{50} was in the range of >1,000 and < 2000 mg/kg bw) and rats (LD_{50} >2,000 mg/kg bw), the inhalation toxicity was not a concern due to the formulation type (no LC_{50} was provided), and the 15 mg/mL product formulation was not a skin irritant. The 15 mg/mL product formulation was an eye irritant, aligning with the SPF factors for inclusion in Schedule 5. I consider that the risk of eye irritation would be sufficiently mitigated as the 15 mg/mL formulation will only be available following advice from a veterinarian, where careful adherence to the label instructions will be emphasised.
- In reference to reproductive and developmental toxicity in rats and rabbits, the reproductive findings included effects on oestrous cycling, mating, conception, litter values and fetal weights. Skeletal abnormalities and variations were observed in fetuses, most notably a constellation of malformed long bones and medially thickened or kinked ribs. An increased incidence of abnormal ossification of various bones was also observed, though this is commonly observed in underweight fetuses associated with maternotoxicity. I note that the teratogenic findings at 100 and 400 mg/kg bw/day were likely reflective of an exaggerated pharmacological effect of an antidiabetic drug inducing hypoglycaemia during pregnancy in a healthy animal model. A NOAEL for embryofetal development was established at 40 mg/kg bw/day.
- I have also considered the repeat-dose oral toxicity studies, noting that the critical effects seen in the liver were increased organ weight in all tested species and hydropic changes in mice and dogs. Effects observed in the kidney were increased organ weight in all tested species and

tubular mineralisation in the rat. I note that the most relevant no-observed-adverse-effect-level (NOAEL) was 30 mg/kg bw/day - determined in two 4-week dietary studies in rats and dogs. In rats, the NOAEL was based on an increase in the incidence and severity of kidney tubular mineralisation in the 100 mg/kg bw/day group (the next higher dose), and in dogs, based on clinical signs, reduced body weight gain and increased kidney weights in the next higher doses of 60/100 mg/kg bw/day group.

- Velagliflozin is unlikely to be genotoxic as demonstrated by an adequate range of assays, both *in vitro* and *in vivo*.
- I have considered that a number of risks in relation to toxicity were not included as part of the HHRA on the basis that there is already sufficient research conducted in both animals and humans in relation to similar drugs of the SGLT2 inhibitor class to allay concerns, i.e.
  - skin sensitisation - not implicated in skin sensitisation
  - carcinogenicity - these compounds are not considered carcinogenic
  - neurotoxicity or immunotoxicity - acute neurotoxicity secondary to hypoglycaemia was considered rare or unlikely.[23,24]
- Regarding the risk to humans through accidental exposure to velagliflozin from home veterinary products, I consider that the human health risk of velagliflozin-associated adverse effects can be adequately mitigated at the time of product registration. I am satisfied that, for the purposes of s 52E(1)(d) of the Act, the APVMA, as the regulator of all veterinary products, will consider the dosage, formulation, labelling, packaging and presentation of velagliflozin-containing products at the time of registration. I note that exposure is most likely to be through the dermal route, with ocular and hand-to-mouth oral also possible. Consistent with the findings of the HHRA, I consider that the risk of oral and dermal toxicity is likely to be low and that the risk from accidental exposure to a child to be sufficiently mitigated through child-resistance closures. Repeated exposure is unlikely but may occur by the dermal route in adult users and is expected to be quantitatively small and note that adequate margins of exposure were achieved when comparing potential human exposure and NOAELs.
- In human studies, I note that the most common adverse effect with other SGLT2 inhibitors has been genital mycotic infections, considered the result of increased and sustained glycosuria facilitating the growth of pathogenic microorganisms. In a field trial with client-owned animals (diabetic cats), there were nine reports related to dermal exposure to owners (product users) but none of these resulted in exposure-related clinical signs. An additional three reports were related to eye exposure in the owners (product users), but only 2 of 3 of these ocular exposures were associated with transient eye irritation. From the data provided to me in the HHRA, I consider that potential risks of the 15 mg/mL product formulation can be sufficiently mitigated through adherence to product label instructions, consistent with the conclusions of the US EPA, EFSA, JMPR and Health Canada PMRA.
- In relation to s 52E(1)(e) of the Act, I am satisfied the potential for misuse or abuse of velagliflozin is limited. In forming this view, I have considered the substance has no established

[23] Mudaliar et al. Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport: From Bench to Bedside

[24] Cuypers, J. et al. SGLT2-INHIBITORS: A NOVEL CLASS FOR THE TREATMENT OF TYPE 2 DIABETES INTRODUCTION OF SGLT2-INHIBITORS IN CLINICAL PRACTICE: Acta Clinica Belgica: Vol 68, No 4 (tandfonline.com)

therapeutic value in humans that would indicate that there is a risk of dependency, abuse, misuse, or diversion into illicit use.

- I note under paragraph 52E(1)(f) of the Act, that the proposed velagliflozin-containing product is for use in companion animals only and is not intended for use in food-producing animals. As such neither an Acceptable Daily Intake (ADI) nor an Acute Reference Dose (ARfD) has been established by the veterinary medicine regulator.

Based on the above considerations and the information provided in the application, I have decided to amend the current Poisons Standard in the manner set out above. The proposed amendment was not referred to an expert advisory committee.

Implementation date

1 October 2023

5.4 Final decision in relation to vadadustat

Final decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made a final decision to amend the current Poisons Standard in relation to vadadustat as follows:[25]

Schedule 4 – New Entry

#VADADUSTAT

Appendix D, clause 5 – New Entry

Item	Poison
35	VADADUSTAT

Index – New Entry

VADADUSTAT

Schedule 4
Appendix D, clause 5

Materials considered

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

- The application with respect to vadadustat.
- Subsection 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.

[25] 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.

- Pursuant to paragraph 52E(2)(a) of the Act, the SPF, and
- the Handbook.

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

In determining that this matter will be a delegate-only decision I have taken into account the information provided in the application, and the matters outlined under Section 52E of the Act and the SPF. In particular I note that:

- Vadadustat is an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor used in the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in patients on chronic maintenance dialysis.
- The proposed amendment to the Poisons Standard is to include an entry for vadadustat in Schedule 4 as a new chemical entity with no clinical experience in Australia.
- In regards to paragraph 52E(1)(a) and (c) of the Act, I note the toxicity of vadadustat can give rise to potential cardiovascular risks, thromboembolic disease, hepatotoxicity, as well as a risk of worsening hypertension and seizures. I believe the potential risks, chiefly hepatotoxicity, are consistent with the SPF factors for Schedule 4.
- The mechanism of action of vadadustat is the stimulation of the patients own erythropoiesis to increase red cell numbers and hence increase haemoglobin. Whilst the half-life of the substance is appreciably short (9.5 hours), physiological effects can last from days to weeks. Furthermore, I am of the opinion that vadadustat as an oral medication with a relatively short half-life has increased potential risk for misuse compared to erythropoiesis stimulating agents (ESAs). I also note that vadadustat is included on WADA's banned substance list. Turning my mind to paragraph 52E(1)(e) of the Act, I am of the opinion that the potential for abuse or misuse of the substance is consistent with Schedule 4 of the Poisons Standard.
- The risk and efficacy profile of vadadustat is consistent with similar substances included in Schedule 4, such as erythropoietin. In considering the relevant SPF factors, I am of the view that the risk of misuse may be similar to ESAs, which are currently included under Appendix D, clause 5. For these reasons I am of the view that additional access restrictions commensurate with Appendix D, clause 5 is appropriate for vadadustat.

On the basis of the above considerations and the information provided in the application, I have decided to amend the current Poisons Standard in the manner set out above. The proposed amendment was not referred to an expert advisory committee.

Implementation date

1 October 2023

6 Amendments to the Poison Standard in relation to New Chemical Entities (NCEs)

The NCEs listed below will be included in the new Poisons Standard that will come into effect on 1 October 2023.

6.1 Concizumab

Schedule 4 – New Entry

CONCIZUMAB

Index – New Entry

CONCIZUMAB

Schedule 4

6.2 Givosiran

Schedule 4 – New Entry

GIVOSIRAN

Index – New Entry

GIVOSIRAN

Schedule 4

6.3 Glofitamab

Schedule 4 – New Entry

GLOFITAMAB

Index – New Entry

GLOFITAMAB

Schedule 4

6.4 Imlifidase

Schedule 4 – New Entry

IMLIFIDASE

Index – New Entry

IMLIFIDASE

Schedule 4

6.5 Mirikizumab

Schedule 4 – New Entry

MIRIKIZUMAB

Index – New Entry

MIRIKIZUMAB

Schedule 4

6.6 Olipudase alfa

Schedule 4 – New Entry

OLIPUDASE ALFA

Index – New Entry

OLIPUDASE ALFA

Schedule 4

6.7 Rimegepant

Schedule 4 – New Entry

RIMEGEPANT

Index – New Entry

RIMEGEPANT

Schedule 4

6.8 Selpercatinib

Schedule 4 – New Entry

SELPERCATINIB

Index – New Entry

SELPERCATINIB

Schedule 4

6.9 Spesolimab

Schedule 4 - New Entry

SPESOLIMAB

Index - New Entry

SPESOLIMAB

Schedule 4

6.10 Tafasitamab

Schedule 4 – New Entry

TAFASITAMAB

Index – New Entry

TAFASITAMAB

Schedule 4

6.11 Tagraxofusp

Schedule 4 – New Entry

TAGRAXOFUSP

Index – New Entry

TAGRAXOFUSP

Schedule 4

6.12 Teclistamab

Schedule 4 - New Entry

TECLISTAMAB

Index - New Entry

TECLISTAMAB

Schedule 4

6.13 Tirbanibulin

Schedule 4 - New Entry

TIRBANIBULIN

Index - New Entry

TIRBANIBULIN

Schedule 4

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