Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

5 October 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

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 Health and Aged Care (the **Delegate**) under regulation 42ZCZN in relation to the proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[1] under subdivision 3D.2 of the Regulations in June 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 in relation to these interim decisions on or before **2 November 2023**.

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

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

Defined terms

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

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

Note: additional terms are also defined for individual decisions.

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

Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #42, June 2023)

Interim decision in relation to bisacodyl

Proposal

The applicant proposed the creation of a new Schedule 2 entry for bisacodyl for oral use except in divided preparations in packs containing 20 tablets or less (the **Proposal**). Bisacodyl is a laxative that is not currently scheduled. The proposed amendment would restrict all oral preparations of bisacodyl to pharmacy sale, except packs of 20 tablets or less which would still be available for purchase from supermarkets and convenience stores.

Interim decision

A Delegate of the Secretary[2] has made an interim decision to create a new entry for bisacodyl in Schedule 2 of the Poisons Standard as follows:[3]

Schedule 2 – New entry

BISACODYL:

a) in divided preparations for oral use **except** in packs containing 20 dosage units or less containing 5 mg or less of bisacodyl per dosage unit; or

b) in divided preparations for rectal use **except:**

(i) in packs containing 12 dosage units or less suppositories containing 10 mg or less of bisacodyl per dosage unit; or

(ii) in packs containing 25 dosage units or less enemas containing 10 mg or less of bisacodyl per dosage unit.

Index – New entry

BISACODYL
Schedule 2

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

[2] Pursuant to regulation 42ZCZN of the Regulations.

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

Materials considered

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

- the application to amend the current Poisons Standard with respect to bisacodyl (the **Application**).
- the 9 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**).
- the advice received from the 42nd meeting of the Advisory Committee on Medicines Scheduling (the **Committee**).
- subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.
- the Therapeutic Guidelines
- the SPF, and
- the Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that bisacodyl be entered in Schedule 2 in the Poisons Standard in the manner set out in my interim decision, with an implementation date of **1 October 2024**.

The Committee agreed on the relevant matters under subsection 52E(1) of the Act, and provided the following reasons for the advice:

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

Risks:

- The risk of intentional or unintentional misuse of bisacodyl is low for the general population but is likely to be higher in vulnerable populations, including older adults, those with eating disorders, children, and people with mental health conditions.
- Unrestricted availability of bisacodyl can contribute to the risks to vulnerable population groups.
- Long-term use of bisacodyl should be managed in a setting with access to a health professional.

Benefits:

- Bisacodyl is a well-tolerated and generally safe stimulant laxative medication for short-term use and can be used for both episodic and chronic constipation.

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

- Bisacodyl is a stimulant laxative for short-term use for the relief of episodic or chronic constipation.
- Clinical guidelines do not recommend the use of bisacodyl and other stimulant laxative medicines as first-line treatment for short-term constipation.

- Bisacodyl products are available in general sale outlets (e.g. supermarkets and convenience stores), as well as in pharmacies, in pack sizes up to 200 tablets.
- For restricted indications, a Pharmaceutical Benefits Scheme (PBS) subsidy is available for 200 tablets.

c) the toxicity of a substance

- Bisacodyl may cause mild adverse effects of abdominal discomfort and pain, including colic and cramps, nausea, vomiting, diarrhoea, blood in stools, dehydration, dizziness and fainting.
- Prolonged overuse of bisacodyl can lead to diarrhoea, with excessive loss of water and electrolytes, particularly potassium, leading to hypokalaemia. Atonic non-functioning colon and reflux constipation may also develop.

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

- Bisacodyl is available in various dosage forms in a wide range of pack sizes.

e) the potential for abuse of a substance

- The risk of abuse is low in the general population but there is likely a high prevalence of misuse in vulnerable populations.
- There is no pharmacological basis for dependency of bisacodyl.

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

- The current unrestricted access to bisacodyl in Australia is inconsistent with the recommended guidelines and regulations of other similar jurisdictions. The proposed changes would bring Australia in line with international regulations.
- The proposed changes may divert consumers who intentionally misuse bisacodyl to senna and other stimulant laxatives that are currently unscheduled and available in larger pack sizes in general sale for similar reasons. Other stimulant laxatives should be considered for scheduling in the future.

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

I have made an interim decision to amend the current Poisons Standard in relation to bisacodyl and create a new Schedule 2 entry for larger pack sizes containing divided preparations for oral and rectal use. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. In relation to s 52E(1)(a) and (b) of the Act, I acknowledge the applicant’s concerns regarding the risk of intentional or unintentional misuse of the substance. Bisacodyl is a stimulant laxative used for the relief of episodic and chronic constipation with a long history of use in Australia and a well-established risk profile. The substance is currently unscheduled and is available in a wide range of pack sizes and various dosage forms, which has the potential to be misused by vulnerable population groups such as older adults, children, and those with eating disorders or other mental health concerns.

I note that the Therapeutic Guidelines does not recommend the use of bisacodyl as a first-line treatment for constipation. Further, long-term use of bisacodyl should be managed in a setting with access to a health professional. In relation to s 52E(1)(c) of the Act, bisacodyl is generally well-

tolerated and may only cause mild adverse effects of abdominal discomfort and pain when used within the recommended dosage. However, prolonged overuse of bisacodyl can lead to diarrhoea with excessive loss of water and electrolytes, particularly potassium, leading to hypokalaemia. It may also lead to development of atonic non-functioning colon. Therefore, reflecting on the factors for pharmacy medicines of the SPF (Schedule 2, factor 1), I consider that access to advice from a pharmacist should be available to maximise the safe use of the medicine.

I agree with the Committee's advice that the current unrestricted access to bisacodyl oral tablets is unwarranted for the treatment of short-term constipation. Aligned with the Committee's advice, I have decided to limit the pack size of bisacodyl oral tablets available for general sale to a maximum of 20 tablets, with each tablet containing 5 mg or less of bisacodyl. This provides consumers with up to 10 days of supply at a maximum daily dose of 10 mg, which is sufficient for the treatment of short-term constipation. Further, this arrangement enables consumers who wish to purchase larger pack sizes of oral bisacodyl tablets to seek advice from a pharmacist or trained pharmacy staff at the point of sale, supporting consumers in selecting the appropriate medicine and promoting the safe use of bisacodyl.

Turning my mind to s 52E (1)(d) of the Act, I have decided to include other dosage forms of bisacodyl, suppositories and enemas, in this proposed Schedule 2 entry. I recognise that despite the current access to bisacodyl being unrestricted, suppositories and enemas containing bisacodyl are currently only available from pharmacies. However, their exclusion from the Schedule 2 entry implies that there are no barriers preventing them from being marketed for general sale in large quantities in the future. While I recognise the risk of misuse of these dosage forms is relatively low, the restriction placed on oral preparations of bisacodyl may divert consumers who misuse bisacodyl to these preparations. After reviewing the relevant products on the market, I have decided to limit the pack size of bisacodyl available for general sale to a maximum of 12 for suppositories and 25 for enemas, with a maximum dosage unit of 10 mg or less bisacodyl. This decision balances the potential risk of misuse of these products but minimises the impact to industry.

In reaching my decision, I have taken into consideration the impact on consumers who use bisacodyl for the relief of chronic constipation. I am of the opinion that consumers with chronic constipation associated with serious diseases and conditions are typically managed by health professionals and many of these consumers access larger pack sizes of bisacodyl with Pharmaceutical Scheme Benefits (PBS) subsidisation. Therefore, their access to bisacodyl will remain unchanged and this amendment will cause minimal inconvenience to consumers.

In consideration of s 52E (1)(e) and (f) of the Act, I have considered the 2018 South Australian Coronial Investigation recommendation that bisacodyl be listed as a pharmacist only medication (Schedule 3) to ensure the provision of professional advice for safe use at the point of sale. I have considered the SPF criteria for Schedule 2 and Schedule 3, and note that while there is a high prevalence of misuse in specific population groups, the risk of misuse in the general population is low. The TGA has only received 23 reports of adverse events related to bisacodyl-containing products from 2013 to 2023, mostly pertaining to abdominal pain, vomiting, and nausea. There is also no pharmacological basis for dependency for bisacodyl. Therefore, I am of the view that bisacodyl best aligns with the scheduling factors for Schedule 2 as set out in the SPF, in particular Schedule 2 factor 3 'the use of the medicine is very unlikely to produce dependency and the medicine is very unlikely to be misused abused or illicitly used'.

I also note the regulatory changes of bisacodyl internationally, especially the UK and New Zealand, which have tightened controls over bisacodyl in recent years. Stimulant laxatives and their accessibility have been the subject of recent reviews in the UK in 2020 (MHRA), and New Zealand in 2021 (Medsafe), both of which recommended tighter control of these substances than the current

unrestricted access in Australia. As such, the decision will bring Australia's regulation of bisacodyl in line with these jurisdictions.

I have considered all 9 public submissions received during the pre-meeting consultation period. The 4 written responses received were fully supportive of the Proposal. Of the submissions received without a written component, 2 were supportive and 3 were opposed to the Proposal.

I have considered the concerns expressed by the Committee and from the Submissions that consumers who misuse bisacodyl may seek to misuse other unscheduled stimulant laxatives such as senna following implementation of this decision. I acknowledge that these substances may present potential risks to public health, similar to bisacodyl, and their scheduling should be considered. However, at present there is insufficient evidence before me in relation to these substances. The scheduling of these substances may be considered if further evidence and information becomes available.

After consideration of the information provided in the application, the public submissions, advice provided by the Committee and the SPF factors, I have made an interim decision to create a new Schedule 2 entry for bisacodyl, with an implementation date of 1 October 2024 to allow industry sufficient time to implement packaging changes in response to the decision.

Implementation date

1 October 2024

Interim decision in relation to olopatadine

Proposal

The applicant proposed the creation of a new Schedule 2 entry for olopatadine when combined with mometasone in aqueous nasal sprays with limitations on dose per actuation and maximum recommended daily dose, for the short-term treatment of allergy conditions in patients aged 12 and over (the **Proposal**). Olopatadine is an antihistamine that is currently available by prescription only (Schedule 4).

Interim decision

A Delegate of the Secretary[4] has made an interim decision to amend the current Poisons Standard in relation to olopatadine as follows:[5]

Schedule 4 – Amend Entry

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

Schedule 2 – New Entry

OLOPATADINE in preparations for nasal use delivering 600 micrograms or less of olopatadine per dose when the maximum recommended daily dose is no greater than 4,800 micrograms for the treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Index – Amend Entry

OLOPATADINE
Schedule 4
Schedule 2

ANTIHISTAMINES
cross reference: ASTEMIZOLE, AZELASTINE, BILASTINE, DESLORATADINE, FEXOFENADINE, LORATADINE, OLOPATADINE, TERFENADINE, CETIRIZINE
Schedule 4
Appendix F, clause 4

Appendix F, clause 4 – Poisons that must be labelled with warning statements and safety directions		
Item	Poison	Warning statement item number
23	Antihistamines not separately specified in this Appendix **except** the following: (a) dermal, ocular, parenteral and paediatric preparations; (b) oral preparations of astemizole, azelastine, bilastine, desloratadine, fexofenadine, loratadine, olopatadine, ternadine or cetirizine	**39** – This medication may cause drowsiness. If affected, do not drive a vehicle, or operate machinery. Avoid alcohol. Or **40** – This medication may cause drowsiness and may increase the effects of alcohol. I effected do not drive a motor vehicle or operate machinery.

[4] Pursuant to regulation 42ZCZN of the Regulations.
[5] 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 olopatadine (the **Application**).
- the 8 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions).**
- the advice received from the 42nd meeting of the Advisory Committees on Medicines Scheduling (the **Committee**).
- the Therapeutic Guidelines
- the Database of Adverse Event Notifications
- the Quality Care Pharmacy Program (QCPP)
- 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.
- the SPF, and
- the Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for olopatadine be amended in the Poisons Standard to create a new Schedule 2 entry which will allow supply of olopatadine as a 'Pharmacy Only' medicine in aqueous nasal sprays with a dose limit of 600 micrograms per actuation and maximum recommended daily dose of 4,800 micrograms, for the short-term treatment of allergic rhinitis in patients aged 12 and over in the manner set out in my interim decision. The Committee recommended an implementation date of **1 February 2024**.

The Committee agreed on the relevant matters under subsection 52E(1) of the Act, and provided the following reasons for the advice:

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

Risks:

- The risk profile for olopatadine is well defined and can be mitigated by packaging and labelling.
- Adverse events include dizziness, dysgeusia, epistaxis, headache, nasal discomfort, oropharyngeal pain, and somnolence.

Benefits:

- Olopatadine is used for the treatment for allergic rhinitis.

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

- Olopatadine has a defined use in allergic rhinitis to treat symptoms, including rhinorrhoea, nasal congestion, sneezing, and nasal itching.

c) the toxicity of a substance

- The toxicity of olopatadine is similar to other over-the-counter products used to treat allergic rhinitis.
- Olopatadine has low toxicity when administered correctly, but somnolence is common.

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

- Nasal spray formulation has low systemic absorption that is favourable for interactions and adverse events.
- Dosage of 600 mcg per spray, recommend 2 sprays per nostril, 240 sprays in container (60 days).

e) the potential for abuse of a substance

- *Nil*

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

- *Nil*

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

I have made an interim decision to amend the current Poisons Standard in relation to olopatadine to create a new Schedule 2 entry which will allow supply of olopatadine as a 'Pharmacy Only' medicine in certain formulations. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I have considered all 8 public submissions received during the pre-meeting consultation period with 3 supportive, 3 partially supportive, and 2 opposing the Proposal. Of the 3 written public submissions, all responses were supportive of down-scheduling, but supported its availability as a 'Pharmacist Only' medicine (Schedule 3) instead of a 'Pharmacy Only' medicine (Schedule 2).

In relation to s 52E(1)(a) and (d) of the Act, olopatadine in nasal preparations has a favourable safety profile despite its recent use in Australia. I acknowledge the main concerns raised by public submissions and the Committee regarding limited safety information being available since it was first registered as a 'Prescription Only' nasal formulation in 2019. However, having reviewed the Database of Adverse Event Notifications (DAEN), I note post-marketing reports of adverse events for olopatadine in combination with mometasone as a nasal preparation have, to date, been minimal.

While I recognise somnolence as a common adverse effect associated with olopatadine, consistent with the Committee's advice, I am confident that this can be managed by appropriate warnings on the label. Pursuant to s 52E(1)(c) of the Act, olopatadine presents a similar safety profile to other over-the-counter substances used to treat the same conditions and offers low systemic absorption as a nasal formulation.

Turning to s 52E(b) of the Act, olopatadine and mometasone as a combination nasal preparation is used for common conditions such as allergic rhinitis and rhinoconjunctivitis. However, I note mometasone nasal sprays and other 'Pharmacy Only' (Schedule 2) entries in the Poisons Standard are limited to the treatment of allergic rhinitis, reserving the treatment of rhinoconjunctivitis to

'Prescription Only' (Schedule 4) medicine. The longstanding availability of over-the-counter products for allergic rhinitis indicates that patients can successfully identify their symptoms. Therefore, it is appropriate to limit the entry to allergic rhinitis only, and not include rhinoconjunctivitis as proposed. In addition, while I am confident many patients can recognise the symptoms of allergic rhinitis and use it appropriately, it is important there is opportunity for certain patients to be screened, assessed and counselled before using an olopatadine and mometasone nasal formulation to ensure it is suitable and used safely. In considering the potential need for a physical nasal examination, I note that additional Schedule 2 training is mandatory for pharmacy assistants to identify when the patient should consult a pharmacist who can then appropriately refer the patient to a medical practitioner if required.

I have considered the Therapeutic Guidelines for the treatment of allergic rhinitis. Intranasal antihistamine use in combination with an intranasal corticosteroid is an appropriate first-line treatment for allergic rhinitis if a patient presents with moderate symptoms. As combination therapy is considered a second-line treatment for mild symptoms, I acknowledge the concern regarding consumers resorting to combination therapy as their primary treatment option. However, it is not unusual for both a first- and second-line treatment options to be available in a pharmacy.

Turning my mind to the SPF, I consider that olopatadine as a monotherapy, or in combination with corticosteroids, both align with the factors for Schedule 2. The quality use of the medicine can be achieved through appropriate labelling, and access to advice from a pharmacist would maximise the safe use of the medicine. I agree with the Committee's advice to list olopatadine separately, rather than define the entry in combination with mometasone. This will provide the flexibility to not restrict other olopatadine-corticosteroid combinations, whereby the efficacy and safety of these combinations can be assessed through the product registration process.

Due to the favourable risk profile, patient screening in a pharmacy setting, and the general ability for consumers to identify and manage risks associated with the use of olopatadine nasal preparations without direct pharmacist oversight, I am satisfied that Schedule 2 is appropriate in addition to relevant warnings on the label (Appendix F).

Consistent with the Therapeutic Guidelines and the Committee's recommendation, I support the proposed requirement that use of olopatadine is restricted to persons '12 years and over'. As olopatadine fits under the 'antihistamine' drug class, I agree with the Committee's proposal to include a cross reference the substance under antihistamines.

I propose the implementation date of 1 February 2024 to prevent unnecessary delay to industry.

Implementation date:

1 February 2024

Interim decisions on proposed amendments referred to the Advisory Committees on Medicines and Chemicals Scheduling in joint session (ACMS-ACCS #34, JUNE 2023)

Interim decision in relation to ibotenic acid

Proposal

The applicant proposed the creation of a new Schedule 4 entry for ibotenic acid for therapeutic use and a new Schedule 7 entry to capture all other use of the substance (the **Proposal**). Ibotenic acid is not currently listed in the Poisons Standard.

Interim decision

A Delegate of the Secretary[6] has made an interim decision to amend the current Poisons Standard in relation to ibotenic acid as follows:[7]

Schedule 9 – New entry

IBOTENIC ACID

Index – New Entry

IBOTENIC ACID
cross reference: MUSCIMOL
Schedule 9

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 ibotenic acid (the **Application**).
- the 8 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**).
- the advice received from the 34th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the **Committee**).
- subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity

[6] Pursuant to regulation 42ZCZN of the Regulations.
[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.

of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

- the SPF, and
- the Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that ibotenic acid be entered in Schedule 9 of the Poisons Standard as follows:

Schedule 9 – New entry

IBOTENIC ACID

Index – New Entry

IBOTENIC ACID
Schedule 9

The Committee also recommended an implementation date of **1 February 2024**.

The Committee agreed on the relevant matters under subsection 52E(1) of the Act, and provided the following reasons for the advice:

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

Risks:

- Ibotenic acid is a psychedelic neurotoxin.
- Ingestion of ibotenic acid can cause multiple adverse effects including altered sensory perception, loss of balance, muscular twitching (often mistaken for convulsions), visual distortions or hallucinations, euphoria, disorientation, agitation, occasional seizures, motor depression, ataxia, and changes in mood, perception, and feelings.
- The long-term effects of use of ibotenic acid are poorly understood.

Benefits:

- There are no benefits; ibotenic acid has no established therapeutic use.

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

- There are no registered medicinal, cosmetic, or therapeutic uses for ibotenic acid in Australia or most international databases.
- Ibotenic acid is used in animal research as a brain lesioning agent (neurotoxic effects) to understand and model Alzheimer's disease and neurodegeneration.
- There is a history of use of crude mushroom extracts containing the substance in some cultures.

c) the toxicity of a substance

- Ibotenic acid is highly neurotoxic.
- Acute oral toxicity in rat (LD50) is 129 mg/kg, in mouse 38 mg/kg.
- GHS hazard classification: category 3 – Acute oral toxicity; H301 Toxic if swallowed.
- European Chemicals Agency (ECHA) – classified as Level 3 Acute toxicity substance.

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

- Nil

e) the potential for abuse of a substance

- There is a high risk for abuse, misuse, or illicit use of ibotenic acid similar to muscimol which is currently listed in Schedule 9.

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

- Ibotenic acid is metabolised to muscimol which is a Schedule 9 poison.
- While ibotenic acid is listed as available for use as an excipient in medical devices on the TGA Ingredients Database, currently there are no registered devices containing ibotenic acid.

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

I have made an interim decision to amend the current Poisons Standard in relation to ibotenic acid and create a new entry in Schedule 9. While I agree with the applicant that the substance should be scheduled, my interim decision is not to create the Schedule 4 and Schedule 7 entries as proposed. The detailed reasons for my decision follow.

The key rationale for this decision is that ibotenic acid is a pro-drug for muscimol, which is also a psychedelic neurotoxin. Ibotenic acid and muscimol are isoxazole derivatives that resemble the neurotransmitters glutamate and gamma-aminobutyric acid (GABA), respectively. Following ingestion, approximately 10-20% of ibotenic acid is metabolised into muscimol. Muscimol is currently included in the Poisons Standard in Schedule 9. As both substances are constituents of the *Amanita muscaria spp.* and produce similar adverse effects, I consider that they require the same scheduling restrictions to access and should also be cross referenced in the index of the Poisons Standard. I am also of the opinion that the considerations of s 52E(1) of the Act, and the SPF factors, strongly align with the scheduling of this substance in Schedule 9.

My decision is in alignment with the Committee's findings on the relevant provisions of section 52E of the Act. It is also in agreement with the concerns of the applicant regarding the necessity for ibotenic acid to be scheduled to prevent accidental poisoning and to protect public health. At the forefront of my decision is the potential for abuse of the substance as set out in s 52E(1)(e) and Schedule 9 factor 2 in the SPF. I agree with the Committee's advice that Schedule 9 is the most appropriate schedule for this substance due to the high propensity for abuse and misuse, and risk of dependency of the substance. The tendency for this substance to be misused stems from the hallucinogenic and euphoric effects following ingestion. In addition to these effects and with respect to s 52E(1)(a), there are significant risks of adverse effects including, altered sensory perception, loss of balance, muscular twitching, visual distortions, seizures, motor depression, and changes in mood, perceptions and feelings. These effects are consistent with the effects experienced following ingestion of muscimol.

In regard to s 52E(1)(c), I acknowledge the applicant's reasoning regarding the toxicity profile of ibotenic acid meeting Schedule 6 factors, with the acute oral toxicity in rat being 129 mg/kg. However, in using the cascading principle, the highly neurotoxic nature and high risk for abuse and misuse make any schedule other than Schedule 9 inappropriate for ibotenic acid. In alignment with s 52E(1)(b) and SPF factor 2 for Schedule 9, I note that despite the long history of use of ibotenic acid via *Amanita muscaria spp.* intake in indigenous ceremonies as mentioned by the applicant, the available evidence in scientific literature pertaining to the therapeutic use of ibotenic acid is largely

contradictory and inconclusive. I note that there have been two studies involving ibotenic acid listed on the Australian New Zealand Clinical Trial database. The first study was withdrawn due to significant adverse events early on in the trial and the second study was withdrawn before it was due to commence. There are also no other uses relating to therapeutics in Australia or in the international pharmaceutical domain. As such, there is currently no established therapeutic value of ibotenic acid and it does not meet the scheduling factors in the SPF for Schedule 4 substances as proposed.

With respect to s 52E(1)(f), I note that the Schedule 9 entry for ibotenic acid is in line with the Food Standards code under Schedule 23 which sets out that *Amanita muscaria spp.* of mushrooms are prohibited for use as a food. I also note the applicant's reference to the TGA Ingredients Database which stipulates that ibotenic acid is approved for use as an excipient in medical devices. However, there are currently no registered products approved for use by the TGA which contain ibotenic acid. I am aware that ibotenic acid is currently used in animal research to study Alzheimer's disease. A Schedule 9 entry will not preclude ibotenic acid from being used in a research setting.

I have considered the 3 written public submissions received during the pre-meeting consultation period. One written response received was in partial support with 2 in opposition of the Proposal. The written submissions raised concerns regarding the high risk to public health as the substance is a neurotoxin and a high risk for accidental poisoning, which in turn makes the proposed entries inappropriate for ibotenic acid. 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. Five responses were received, with 3 supportive, 1 partially supportive and 1 opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were generally in support of scheduling ibotenic acid.

The proposed Appendix E and F entries which stipulate labelling requirements are not required as these appendices do not apply to Schedule 9 substances.

I have included in my interim decision an implementation date of 1 February 2024, as there is currently no therapeutic use of the substance that would be impacted by this decision.

Implementation date

1 February 2024

Interim decision in relation to amygdalin and hydrocyanic acid

Proposal

The applicant proposed an exemption for the Schedule 10 and Schedule 4 entries for amygdalin and hydrocyanic acid, respectively, when in ARTG listed preparations containing Wild Cherry Bark (*Prunus serotina*) (the **Proposal**). Amygdalin and hydrocyanic acid are naturally occurring constituents of Wild Cherry Bark which is used in traditional medicine as an oral treatment for various self-limiting conditions, including cough suppression. Amygdalin is currently listed in the Poisons Standard as a Schedule 10 substance for therapeutic use. Hydrocyanic acid is currently listed in the Poisons Standard as a Schedule 7 substance except when used as a therapeutic (Schedule 4).

Interim decision

A Delegate of the Secretary[8] has made an interim decision not to amend the current Poisons Standard in relation to amygdalin and hydrocyanic acid.

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 amygdalin and hydrocyanic acid (the **Application**).
- the 36 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**).
- the advice received from the 34th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the **Committee**).
- subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.
- the Delegate's final decision to not amend the Poisons Standard in relation to amygdalin and hydrocyanic acid on 20 December 2021 and the materials considered in making that decision (the **2021 final decision**).
- the SPF, and
- the Handbook.

[8] Pursuant to regulation 42ZCZN of the Regulations.

Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entries for amygdalin and hydrocyanic acid remain appropriate.

The Committee agreed on the relevant matters under subsection 52E(1) of the Act, and provided the following reasons for the advice:

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

Risks:

- Wild Cherry Bark contains both amygdalin and hydrocyanic acid as natural constituents. Hydrocyanic acid (a solution of hydrogen cyanide in water) is highly toxic, with significant variability of the toxic dose between individual persons. When amygdalin is metabolised it is converted to hydrocyanic acid.
- There is a relative degree of uncertainty relating to processing of Wild Cherry Bark and the accumulative exposure from dietary and therapeutic sources. Health risks are amplified in compounded substances.
- Increased access to products containing amygdalin may promote the inappropriate use of amygdalin for the treatment of conditions such as cancer and COVID-19.
- Increased access to Wild Cherry Bark has the potential to dissuade consumers from seeking medical attention for conditions.
- Ingestion of Wild Cherry Bark poses greater risks of toxicity in children.
- The difficulty determining a reasonable daily intake of amygdalin and hydrocyanic acid, given potential dietary and therapeutic consumption.
- Quality control would be difficult to reliably achieve due to the high variability of amygdalin and hydrocyanic acid content in Wild Cherry Bark.

Benefits:

- Wild Cherry Bark is generally used as a complementary therapy for various self-limiting conditions.
- There is a limited evidence base, which is mainly within the Traditional Medicines paradigm.

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

- Wild Cherry Bark is mainly used in oral dosage forms for cough suppression.

c) the toxicity of a substance

- Hydrocyanic acid arrests cellular respiration and is highly toxic at low doses.
- Wild cherry bark with an amygdalin content of 5 mg, can potentially yield 11 mg of hydrocyanic acid.
- A wide range of expert committees have concluded that an oral intake of 5-20 mg/day amygdalin in a 60 kg adult is likely to be low risk.
- Issues were noted in the application relating to the calculation of total hydrocyanic acid concentration in Wild Cherry Bark. The Committee was unclear whether the

calculation was inclusive of endogenous hydrocyanic acid as well as its production from the metabolism of amygdalin.

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

- Wild Cherry Bark can be made into several oral dose forms.
- Labelling recommendations outlined by the applicant for Wild Cherry Bark products include:
  1) for adult use
  2) not for use in pregnancy, and
  3) if symptoms persist, seek professional advice.

e) the potential for abuse of a substance

- There is evidence of amygdalin-containing products being misused for use as an unapproved treatment for cancer. The risk of diversion to cancer therapy is low due to limits on dosage. There is no evidence that amygdalin can treat or prevent cancer.
- The bioavailability of hydrocyanic acid and amygdalin present in Wild Cherry Bark can vary considerably. This compounds the risk of exposure to toxic levels to consumers (which also has high variability).

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

- No laboratories in Australia currently test for hydrocyanic acid due to safety. Current testing lacks the sensitivity to detect near 0% concentrations of these substances.
- Unscheduled products containing Wild Cherry Bark would have no controls on packaging and labelling through State and Territory legislation.
- Hydrocyanic acid fumes can occur when brewed in tea preparations due to the low boiling point of hydrocyanic acid (26-35 ºC).

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

I have made an interim decision to not amend the current Poisons Standard in relation to amygdalin and hydrocyanic acid. Both amygdalin and hydrocyanic acid scheduling have been considered over recent years in preparations for human therapeutic use. I have made this decision given the lack of new information addressing the risks to public health from the toxicity of these substances, which outweigh the potential benefits when used in traditional medicines.

The detailed reasons for my decision are as follows.

The Proposal would allow for preparations containing Wild Cherry Bark (which naturally contains amygdalin and hydrocyanic acid) to be exempt from current access restrictions when listed on the ARTG and labelled to exclude use in children or pregnant females. I agree with the Committee's findings on the relevant provisions of section 52E of the Act, that it is not appropriate to down-schedule amygdalin and hydrocyanic acid from Schedule 10 and Schedule 4, respectively, to be unscheduled. Making such Wild Cherry Bark preparations available for general sale would not meet the explanation of 'with reasonable safety' as outlined in the Handbook.

I have considered the 21 written public submissions received during the pre-meeting consultation period. 12 written responses received were fully supportive of the Proposal, 4 partially supportive and 5 opposed. 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.

36 responses were received, with 22 supportive, 4 partially supportive and 10 opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were generally in favour of the Proposal.

History of misuse of amygdalin

As outlined in the 2021 final decision, amygdalin has, in the past, been inappropriately promoted and used as an alternative cancer treatment, with unproven claims for use in treating or preventing cancer. I have again considered the independent scheduling evaluation report published in October 2020 documenting 5 case reports of amygdalin toxicity in adults with daily oral amygdalin (also known as laetrile) doses ranging from approximately 420 mg to 1.5 g used in the treatment of cancer. In relation to the SPF criteria pertinent to s 52E(1)(e) of the Act, the risk of misuse or diversion of amygdalin aligns with the SPF factors for Schedule 10. I note multiple Submissions stating that the likelihood of intentional misuse of preparations containing Wild Cherry Bark is unlikely given the low concentration of amygdalin. I also note the Submissions in support of the Proposal that recommend restricting availability to registered herbalists to ameliorate risks associated with misuse and diversion of Wild Cherry Bark preparations. In making this decision, I note that the Application provided no evidence that the risk of misuse or diversion of amygdalin for cancer treatment is reduced in Wild Cherry Bark preparations. I am of the opinion that, while the risk of inappropriate use and misuse may be low in these preparations, no evidence has been provided that the risk is negligible. I also note the public submissions received in support of the Proposal which proposed restrictions on dispensing to registered herbalists to reduce risks to the public. Such a proposal is inconsistent with the proposal to unschedule these substances in Wild Cherry Bark preparations. Unscheduled access to Wild Cherry Bark preparations provides access without oversight of any healthcare professional. As such, if oversight is considered necessary to prevent potential misuse, then general sale is not appropriate.

Considerations of therapeutic use and toxic dose

In weighing the considerations of s 52E(1)(a), (b), (c), and (d), I am of the view that the therapeutic benefits outlined in the Proposal do not outweigh the potential risks of toxicity from both amygdalin and hydrocyanic acid in Wild Cherry Bark when used in traditional medicine.

I have considered responses received from various peak bodies, such as Complementary Medicines Australia, Torrens University Australia and the Australian Traditional Medicine Society highlighting the historic use of Wild Cherry Bark as a traditional medicine for its antitussive properties with no reports of adverse events. Reflecting on these submissions, I am of the opinion that the lack of adverse events reported in Australia for medicines containing Wild Cherry Bark is due to the Schedule 10 listing of amygdalin in the Poisons Standard and the requirement of 0% amygdalin content in the Permissible Ingredients Determination, ensuring that there are no medicines containing Wild Cherry Bark in Australia. In addition, outside of the traditional medicine paradigm, the Application has not provided substantial evidence of established therapeutic value or efficacy from scientific evidence. I also note that the use of Wild Cherry Bark in traditional medicines is primarily for the treatment of self-limiting conditions.

In relation to the risk of toxicity from amygdalin and hydrocyanic acid in Wild Cherry Bark, and the proposed limits of a maximum recommended daily dose of 5 mg for amygdalin and 0.3 mg hydrocyanic acid, insufficient evidence was provided in the Application to assure me that these limits would not produce toxicity following exposure. I note the Submissions from multiple peak bodies, including the Naturopaths and Herbalists Association of Australia, stating that there is insufficient evidence of health risks when the amygdalin dose is below 5 mg. However, I am in agreement with the Committee's advice that the bioavailability of hydrocyanic acid and amygdalin present in Wild

Cherry Bark can vary considerably, and that this variability increases the risk of consumer exposure to toxic levels. Furthermore, amygdalin levels can vary substantially in Wild Cherry Bark, giving rise to greater hydrocyanic acid levels through amygdalin hydrolysis. It is also important to note that Wild Cherry Bark contains both amygdalin (62-242 mg/kg dried bark) and hydrocyanic acid (100-520 mg/kg dried bark) (Data provided by the Applicant and noted in the Application).

Taking the contribution of both endogenous levels of hydrocyanic acid and that from the hydrolysis of amygdalin, consumption of approximately 21 g of Wild Cherry Bark with an amygdalin content of 5 mg could release approximately 0.3 mg of hydrocyanic acid via hydrolysis, together with 10.7 mg of hydrocyanic acid that is already present in the bark. This could potentially yield up 11 mg of hydrocyanic acid. The Application did not factor endogenous levels of hydrocyanic acid into their calculations for total hydrocyanic acid within Wild Cherry Bark, significantly increasing the risk of cyanide poisoning from these preparations. As a result, the calculations provided in the Application do not assure me that the proposed recommended daily doses would correlate to a safe total hydrocyanic acid level. Therefore, I am not satisfied that the risks of toxicity are sufficiently mitigated to justify changing the schedule entries for amygdalin and hydrocyanic acid.

On consideration of the SPF factors, I am of the view that the risk profile of these substances is consistent with Schedule 4, factor 5 (for therapeutic use of hydrocyanic acid) and Schedule 10 factors (for amygdalin) of the SPF. This is because the margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical intervention to minimise the risk of using the substance.

In making this decision, I have also considered the implications of implementing a concentration cut-off for amygdalin and hydrocyanic acid in Wild Cherry Bark preparations, and the impact this will have on quality control of any products. As emphasised above, the potential for high variability of amygdalin and hydrocyanic acid levels in Wild Cherry Bark would require stringent and sensitive methods for the testing of amygdalin and hydrocyanic acid content. I am in agreement with the Committee's advice that Wild Cherry Bark product quality control would be difficult to reliably achieve due to the high variability of amygdalin and hydrocyanic acid content in Wild Cherry Bark. In making my decision, investigation into the current testing practices for detection of hydrocyanic acid has revealed that there is a current lack of available hydrocyanic acid testing nationally, and where available, the techniques carry considerable health risk to those conducting the testing, while not being adequately robust or sensitive in their detection. Therefore, I am of the opinion that industry is not capable at this time to undertake reproducible testing of amygdalin and hydrocyanic acid content in Wild Cherry Bark preparations if a concentration cut-off were implemented in the Poisons Standard.

The food-therapeutic interface

In relation to s 52E(1)(f) of the Act, I acknowledge the Submission from Complementary Medicines Australia regarding the need for a reasonable limit for amygdalin, given that the current Schedule 10 entry prohibits all Wild Cherry Bark preparations containing amygdalin, and does not adequately consider the presence of amygdalin in some plant foods and medicines.

While I acknowledge from the Submissions that a concentration cut-off for amygdalin or hydrocyanic acid could be established based on food limits set by the Australian New Zealand Food Standards (FSANZ), I emphasise that the calculations for determining a 'safe dose' are different for calculating a permissible level in food versus for a therapeutic use. The FSANZ food limits (which considers 5 mg/kg amygdalin as safe) are based on the Acute Reference Dose (ARfD) following ingestion over a short period of time e.g. during one meal or one day. Conversely, therapeutics are consumed at a high dose, daily, or at regular intervals during the day, and consistently over a long period of time. As such, adopting a similar permissible concentration based on the FSANZ food limit is not equivalent to

the risk of toxicity for these substances when in therapeutic preparations. Further, a concern when assessing the risk of toxicity of the Proposal is the consumption of amygdalin-containing foods e.g. stone fruit kernels and some seeds, in addition to the regular, and possibly chronic, ingestion of amygdalin and hydrocyanic acid from treatments containing Wild Cherry Bark. I agree with the Committee's advice that there is insufficient evidence that combined consumption of hydrocyanic acid from dietary and therapeutic sources will not result in a toxic dose in adults (e.g. 0.5 to 3.5 mg/kg body weight– purported lethal dose) or children.

In relation to s 52E(1) (a) of the Act, I agree with the Committee that the health risks are amplified in compounded substances. I would like to clarify that this refers to compounding regarding the risks posed by these substances being significantly amplified when consumed as a both a therapeutic and when consumed from dietary sources.

In summary, the scheduling of both amygdalin and hydrocyanic acid have been considered in recent years in preparations for human therapeutic use. Since the last scheduling consideration, insufficient new evidence has been provided establishing that the therapeutic benefits of Wild Cherry Bark preparations outweigh the risks of down-scheduling amygdalin and hydrocyanic acid. As such, the proposed amendments to the Poisons Standard regarding amygdalin and hydrocyanic acid are inconsistent with the SPF and pose an unfavourable balance of the risks and benefits to the public. I have therefore decided not to amend the existing scheduling of either amygdalin or hydrocyanic acid.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au