Australian Government
Department of Health
Therapeutic Goods Administration

Notice of amendments to the Poisons Standard in relation to New Chemical Entities (NCEs) and Delegate-only decisions

13 April 2022

TGA Health Safety Regulation

Contents

1 Notice of Decisions to amend the current Poisons Standard

This web publication constitutes a notice for the purposes of regulation 42ZCZX of the *Therapeutic Goods Regulations 1990* (the Regulations), in accordance with which this notice publishes the:

- decisions made by a delegate of the Secretary pursuant to regulations 42ZCZU;
- reasons for those final decisions; and
- date of effect of those decisions.

2 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 June 2022.

2.1 Belzutifan

Schedule 4 – New Entry

BELZUTIFAN

Index – New Entry

BELZUTIFAN

Schedule 4

2.2 Diroximel fumarate

Schedule 4 - New Entry

DIROXIMEL FUMARATE

Index - New Entry

DIROXIMEL FUMARATE

Schedule 4

2.3 Enfortumab vedotin

Schedule 4 - New Entry

ENFORTUMAB VEDOTIN

Index - New Entry

ENFORTUMAB VEDOTIN

Schedule 4

2.4 Lurbinectedin

Schedule 4 - New Entry

LURBINECTEDIN

Index - New Entry

LURBINECTEDIN

Schedule 4

2.5 Mavacamten

Schedule 4 - New Entry

MAVACAMTEN

Index - New Entry

MAVACAMTEN

Schedule 4

2.6 Ponatinib

Schedule 4 – New Entry

PONATINIB

Index – New Entry

PONATINIB

Schedule 4

2.7 Somapacitan

Schedule 4 - New Entry

SOMAPACITAN

Index - New Entry

SOMAPACITAN

Schedule 4

3 Amendments to the Poisons Standard made as delegate-only decisions

3.1 Final decision in relation to inpyrfluxam

Final decision

Pursuant to regulation 42ZCZU of the Therapeutic Goods Regulations 1990 (Cth) (the **Regulations**) a Delegate of the Secretary has made a final decision to amend the current Poisons Standard in relation to inpyrfluxam as follows:

Schedule 6 – New entry

INPYRFLUXAM

Index – New entry

INPYRFLUXAM

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 inpyrfluxam;
- Subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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 (e) the potential for abuse of a substance;
- Pursuant to paragraph 52E(2)(a) of the Act, the Scheduling Policy Framework 2018 (**SPF**); and
- The Scheduling handbook: Guidance for amending the Poisons Standard (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 from the applicant (Australian Pesticides and Veterinary Medicine Authority (APVMA)), and the matters outlined under Section 52E of the Act and the SPF. In particular I note that:

- In relation to paragraph 52E(1)(a) of the Act, the proposed amendment to the Poisons Standard is to include a new entry for inpyrfluxam in Schedule 6, based upon benefits to the agricultural industry from the introduction of a novel fungicide. In its application, the regulator (APVMA) provided a Human Health Risk Assessment (HHRA) which concluded that the risks to human health and safety posed by this substance are acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994)*.
- In relation to paragraph 52E(1)(b) of the Act, inpyrfluxam is a fungicide of the pyrazole carboxamide class. Inpyrfluxam is a new agricultural technical grade active constituent

(TGAC) in Australia for use on potato and banana crops. Products containing inpyrfluxam have been approved in Japan, USA and Canada and it is currently under consideration for approval in the EU, Brazil and Argentina.

- In relation to paragraph 52E(1)(c) of the Act, the application provided toxicity data about the TGAC and an agricultural product formulation containing inpyrfluxam at 400 g/L.
- The toxicity data for the TGAC indicated that inpyrfluxam is of moderate to high acute toxicity by the oral route (LD_{50} between 50 - 180 mg/kg bw in rats), and of low acute toxicity by dermal (LD_{50} >2000 mg/kg bw in rats) and inhalational routes (LD_{50} >2610 mg/m^3/4h in rats). It is a slight eye irritant but not a skin irritant or sensitiser. Repeat-dose, chronic toxicity studies in mice, rats and dogs identified key adverse effects upon the adrenal gland (zona fasciculata cell vacuolation) and optic nerve (degeneration). Inpryfluxam was not genotoxic in a battery of *in vitro* and *in vivo* assays, and was not carcinogenic in chronic toxicity/carcinogenicity studies in mice and rats, respectively. Inpyrfluxam was not considered a reproductive or developmental toxicant. Neurotoxicity in rats (reduced motor activity and body temperature) occurred at high acute concentrations (100 mg/kg bw) whereas in dogs, optic nerve damage was observed in subchronic studies (90 day and 1 year) at doses ≥160 mg/kg bw/day.
- An Acceptable Daily Intake (ADI) of 0.06 mg/kg bw/d has been established by the APVMA based on adrenal effects in a 1-year dog study and an ARfD of 0.3 mg/kg bw based on transiently reduced motor activity in an acute neurotoxicity study in rats. Overall, the toxicity profile for inpyrfluxam (TGAC) is consistent with a Schedule 6 entry.
- Toxicity data for a product containing 400 g/L inpyrfluxam, indicated that at this concentration, it is of moderate acute toxicity by the oral route (LD_{50} between 300 - 2000 mg/kg bw in rats) and of low acute toxicity by the dermal (LD_{50} >2000 mg/kg bw in rats) and inhalational routes (LD_{50} >2210 mg/m3/4h in rats). It is a slight eye irritant but not a skin irritant or sensitiser. Overall, the toxicity profile of inpyrfluxam in this product is also consistent with a Schedule 6 entry, and no concentration cut-off or exemptions to a lower Schedule could be identified at this time.
- I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the dosage (application rate), formulation, labelling, packaging and presentation of any commercial products.
- In relation to paragraph 52E(1)(e) of the Act, the substance has no human therapeutic value or significant pharmacological effect that would indicate a risk for diversion, misuse or abuse.

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.

Date of effect

1 June 2022

3.2 Final decision in relation to dimpropyridaz

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 dimpropyridaz as follows:

Schedule 6 – New Entry

DIMPROPYRIDAZ **except** when included in Schedule 5.

Schedule 5 – New Entry

DIMPROPYRIDAZ in preparations containing 13 per cent or less of dimpropyridaz.

Index – New Entry

DIMPROPYRIDAZ

Schedule 6
Schedule 5

Materials considered

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

- The application to amend the current Poisons Standard with respect to dimpropyridaz;
- 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 (e) the potential for abuse of a substance;
- The SPF, pursuant to paragraph 52E(2)(a) of the Act; 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 from the applicant (Australian Pesticides and Veterinary Medicine Authority (APVMA)), and the matters outlined under Section 52E of the Act and the SPF. In particular I note that:

- In relation to paragraph 52E(1)(a) of the Act, the proposed amendment to the Poisons Standard is to include new entries for dimpropyridaz in Schedule 5 and Schedule 6, based upon benefits to the agricultural industry from the introduction of a novel insecticide. In its application, the regulator (APVMA) provided a Human Health Risk Assessment (HHRA) which concluded that the risks to human health and safety posed by this substance are acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994)*.
- In relation to paragraph 52E(1)(b) of the Act, dimpropyridaz is an insecticide of the pyrazole carboxamide class. Other members of this class are included in Schedule 5 (fluxapyroxad) and Schedule 6 (tebufenpyrad). Dimpropyridaz is a new agricultural technical grade active constituent (TGAC) in Australia and has not previously been approved overseas.

- In relation to paragraph 52E(1)(c) of the Act, the application provided toxicity data about the TGAC and an agricultural product formulation containing dimpropyridaz at 120 g/L (equivalent to 13%).
- The toxicity data for the TGAC indicated that dimpropyridaz is of moderate acute toxicity by the oral route (LD_{50} 300 to 500 mg/kg bw in rats), and low acute toxicity by the dermal (LD_{50} >2000 mg/kg bw in rats) and inhalation routes (LD_{50} >5590 mg/m^3 in rats). It is a slight skin and eye irritant in rabbits but is not a skin sensitiser in the mouse (local lymph node assay, LLNA). Repeat-dose, chronic toxicity studies in mice, rats and dogs indicated that dimpropyridaz intake was generally associated with reductions in body weight and some mild, reversible hepatotoxicity. While dimpropyridaz was maternotoxic, it was not a developmental toxicant in either rats or rabbits. It was not acutely neurotoxic in rats, and it was not genotoxic in a battery of *in vitro* and *in vivo* assays. It was not a human-relevant carcinogen in rats and it was not carcinogenic in mice.
- An Acceptable Daily Intake (ADI) of 0.2 mg/kg bw/d has been established by the APVMA based on a 10% reduction in body weight, reduced body weight gain and hepatic lipofuscinosis in near lifetime dietary studies in rats. An ARfD was considered to be unnecessary due a lack of acute neurotoxicity, and reproductive and developmental effects following a single exposure event. Overall, the toxicity profile for dimpropyridaz (TGAC) is consistent with a Schedule 6 entry.
- Toxicity data for a product containing 120 g/L dimpropyridaz (equivalent to a 13 percent solution), indicated that at this concentration it is of low acute toxicity by the oral (LD_{50} >2000 mg/kg bw in rats), dermal (LD_{50} >2000 mg/kg bw in rats) and inhalation routes (LD_{50} >5180 mg/m^3 in rats). The product is a slight eye and skin irritant in rabbits but showed no skin sensitisation in mice. Overall, the toxicity profile of dimpropyridaz in this product is consistent with a Schedule 5 entry for preparations containing 15 percent or less of the active substance.
- I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the dosage (application rate), formulation, labelling, packaging and presentation of any commercial products.
- In relation to paragraph 52E(1)(e) of the Act, the substance has no human therapeutic value or significant pharmacological effect that would indicate a risk for diversion, misuse or abuse.

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.

Date of effect

1 June 2022

3.3 Final decision in relation to aminocyclopyrachlor

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 aminocyclopyrachlor as follows:

Schedule 5 – Amended Entry

AMINOCYCLOPYRACHLOR **except** in preparations containing 25 per cent or less of aminocyclopyrachlor.

Materials considered

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

- The application to amend the current Poisons Standard with respect to aminocyclopyrachlor;
- 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 (e) the potential for abuse of a substance;
- The SPF, pursuant to paragraph 52E(2)(a) of the Act; 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 from the applicant (Australian Pesticides and Veterinary Medicine Authority (APVMA)), and the matters outlined under Section 52E of the Act and the SPF. In particular I note that:

- In relation to paragraph 52E(1)(a) of the Act, the regulator (APVMA) has provided a Human Health Risk Assessment (HHRA) which concluded that the risks to human health and safety posed by this substance (at 240 g/L) are acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act (1994)*.
- In relation to paragraph 52E(1)(b) of the Act, aminocyclopyrachlor is a herbicide of the pyrimidine carboxylic acid class, used for selective control of weeds and invasive species. Products containing aminocyclopyrachlor are registered in the USA and Canada, either as a sole active ingredient or in combination with other active ingredients. Although there were no products containing the substance available in Australia at the time, the agricultural technical grade active constituent (TGAC) aminocyclopyrachlor, was previously placed into Schedule 5 of the Poisons Standard in 2012 due to evidence of slight eye irritation, with no cut-off included. Moreover, the TGAC was of low acute toxicity by the oral, dermal and inhalational routes, was not a skin irritant or sensitiser, there was no evidence of adverse effects on reproduction or development, and an absence of neurotoxicity, carcinogenicity, genotoxicity and immunotoxicity.
- In relation to paragraph 52E(1)(c) of the Act, the proposed amendment to the Poisons Standard will exempt aminocyclopyrachlor from scheduling control when present in preparations at a concentration of 25 per cent or less, based upon the toxicity profile of a product containing 240 g/L of the TGAC. Aminocyclopyrachlor was previously included in Schedule 5 with no concentration limits. However, new data indicate a lack of eye irritation and therefore the toxicity profile would fall below the thresholds for inclusion in Schedule 5 as outlined in the SPF.
- I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the dosage (application rate), formulation, labelling, packaging and presentation of any commercial products.

- The substance has no human therapeutic value or significant pharmacological effect that would indicate a risk for diversion, misuse or abuse (52E(1)(e)).

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.

Date of effect

1 June 2022

3.4 Final decision in relation to monoclonal antibodies

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 casirivumab, cilgavimab, imdevimab, regdanvimab and tixagevimab as follows:

Schedule 4 – New Entries

CASIRIVIMAB.

CILGAVIMAB.

IMDEVIMAB.

REGDANVIMAB.

TIXAGEVIMAB.

Index – New Entries

CASIRIVIMAB

Schedule 4

CILGAVIMAB

Schedule 4

IMDEVIMAB

Schedule 4

REGDANVIMAB

Schedule 4

TIXAGEVIMAB

Schedule 4

Materials considered

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

- The SPF, pursuant to paragraph 52E(2)(a) of the Act; 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 SPF. In particular, I note that:

- These medicines have been assessed by the Therapeutic Goods Administration as meeting the Scheduling Policy Framework for Schedule 4 (prescription-only medicine) substances in the Poisons Standard.
- As members of the monoclonal antibody class of medicines, these five substances are already regarded as prescription-only medicines under the Schedule 4 group entry for that class in the Poisons Standard:

  MONOCLONAL ANTIBODIES for therapeutic use **except**:

  a) in diagnostic test kits; or

  b) when separately specified in these Schedules.

- However, given their use in the treatment of COVID-19 and that they are specified products in the Australian Register of Therapeutic Goods (ARTG), I have decided that it will be prudent to include specific listings for each of these medicines in Schedule 4.

Based on the above considerations, I have decided to amend the current Poisons Standard in the manner set out above. The proposed amendments were not referred to an expert advisory committee.

Date of effect

1 June 2022