Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

14 September 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 regulation 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 October 2022.

2.1 Asciminib

Schedule 4 – New Entry

ASCIMINIB

Index – New Entry

ASCIMINIB

Schedule 4

2.2 Faricimab

Schedule 4 - New Entry

FARICIMAB

Appendix L – New Entry

FARICIMAB: Warning statement 76 (Do not become pregnant during use or within 3 months of stopping treatment).

Index - New Entry

FARICIMAB

Schedule 4
Appendix L

2.3 Mobocertinib

Schedule 4 - New Entry

MOBOCERTINIB

Index - New Entry

MOBOCERTINIB

Schedule 4

2.4 Osilodrostat

Schedule 4 – New Entry

OSILODROSTAT

Index – New Entry

OSILODROSTAT

Schedule 4

2.5 Pemigatinib

Schedule 4 - New Entry

PEMIGATINIB

Index - New Entry

PEMIGATINIB

Schedule 4

2.6 Vosoritide

Schedule 4 - New Entry

VOSORITIDE

Index - New Entry

VOSORITIDE

Schedule 4

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

3.1 Final decision in relation to bovine herpesvirus-1 vaccine

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 bovine herpesvirus-1 vaccine as follows:

Schedule 4 – Amend entry

VACCINES for veterinary live vaccine **except:**

a) poultry vaccines;

b) pigeon pox vaccine;

c) scabby mouth vaccine; ~~or~~

d) bovine ephemeral fever vaccine; or

e) bovine herpesvirus-1 vaccine.

Materials considered

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

- The application to amend the current Poisons Standard with respect to bovine herpes-1 vaccine;
- 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 exempt the bovine herpesvirus-1 vaccine from the Schedule 4 entry for veterinary live vaccines, based upon the use pattern and adverse event profile of the currently registered bovine herpesvirus-1 live virus vaccine. 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, bovine herpesvirus-1 vaccine was registered for use in Australia in 2000 for the prevention of bovine herpesvirus-1 infection and the clinical syndrome infectious bovine rhinotracheitis (IBR). It is used to prevent and protect cattle from bovine herpesvirus and is administered by the intranasal route as part of the standard vaccination protocol used in feedlots or for dairy calves.
- In relation to paragraph 52E(1)(c) of the Act, I note the applicant has provided the following toxicity and safety information to support exemption from Schedule 4 of the Poisons Standard:

- The currently registered product is administered prior to diagnosis of disease, typically as part of routine vaccination protocol, such as at weaning or feedlot induction. I note that producers have been safely and effectively administering it to cattle for many years and this generally occurs without diagnosis, management or monitoring by veterinarians. Furthermore, no adjunctive therapy or evaluation is required for the appropriate use of the product as farmers are accustomed to administering vaccines (minimal training required) to livestock without the advice and instruction of a veterinarian.
- I recognise that the risk of needle stick injury or accidental self-injection is reduced as compared to other cattle vaccines, as a needle is only used when reconstituting the vaccine whereas delivery of the dose is via the intranasal route using a specific applicator.
- Between 2000 and 2020 no human adverse experiences (reported via the Adverse Experience Reporting Program (AERP)) were reported in Australia for the live bovine herpesevirus-1 vaccine. Considering that more than 12 million doses were sold in this period, this vaccine has a demonstrable safety profile. In addition, the company producing the vaccines has indicated that as a modified live vaccine, there is already a sufficient safety margin in place to support the continued and routine administration by non-veterinarians.
- There are no known interactions involving the bovine herpesvirus-1 vaccine that would require monitoring or intervention by a veterinarian, or any evidence of communal harm e.g. microbial resistance, from the use of this vaccine. I agree with the APVMA that based on the data, there are no foreseeable communal harms from use of this vaccine.

· I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the applicable dosage, 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 that would indicate a risk of dependency, misuse, abuse or diversion into illicit use.

On the basis of the above considerations and the information provided in the application, I consider that the bovine herpesvirus-1 vaccine does not meet the Schedule 4 scheduling factors, and therefore 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 October 2022

3.2 Final decision in relation to cyclobutrifluram

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 cyclobutrifluram as follows:

Appendix B – New Entry

Substance	Date of entry	Reason for listing	Area of use
CYCLOBUTRIFLURAM	October 2022	a	1.3, 1.3.1

Index – New Entry

CYCLOBUTRIFLURAM

Appendix B, Part 3

Materials considered

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

- The application to amend the current Poisons Standard with respect to cyclobutrifluram;
- 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 that the Secretary considers necessary to protect public health;
- 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 a new entry for cyclobutrifluram in Appendix B, thereby exempting the substance from any requirements that are imposed by scheduling, based upon benefits to the agricultural industry from the introduction of a new nematicide. 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 cyclobutrifluram is a nematicide for the control of plant parasites, and belongs to the pyridine-3-carboxamide chemical class. Its mode of action is as a selective inhibitor of succinate dehydrogenase (complex II) disrupting ATP production in nematode and fungal mitochondria. The substance has not previously been considered for inclusion in the Poisons Standard.
- In relation to paragraph 52E(1)(c) of the Act, the application provided data for cyclobutrifluram which indicated that the toxicity profile is not consistent with inclusion into the Schedules, based on its very low acute oral toxicity (LD_{50} > 5000 mg/kg bw), low dermal toxicity (LD_{50} > 2000 mg/kg bw), and low inhalational toxicity (LC_{50} > 4080 mg/m^3/4h). While cyclobutrifluram is a slight eye irritant, it is not a skin irritant or sensitiser.

- Cyclobutrifluram did not adversely affect reproduction, development survival in a rat multigenerational study at doses up to 43.1 mg/kg bw/day, the highest dose tested. Cyclobutrifluram was neither teratogenic nor maternotoxic in a prenatal development study in rats at oral doses up to 250 mg/kg bw/d, the highest dose tested. Cyclobutrifluram was not teratogenic in a rabbit prenatal development study at doses up to 125 mg/kg bw/d, the highest dose tested.
- Cyclobutrifluram was not found to be genotoxic in validated battery of studies and was not carcinogenic in mice and rats. Furthermore, it was not an acute neurotoxicant in rats.
- I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the dosage, 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 that would indicate a risk of dependency, misuse, abuse or diversion into illicit use.
- I also noted for the purposes of paragraph 52E(1)(f) of the Act, that an acceptable daily intake (ADI) for cyclobutrifluram of 0.08 mg/kg bw/d has been established based on a No Observed Adverse Effect Level (NOAEL), from non-tumorigenic effects in a 104-week dietary toxicity and carcinogenicity study in rats. An acute reference dose (ARfD) was not considered to be necessary due to its low oral toxicity and absence of neurological effects or development toxicity after a single dose.

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 October 2022

3.3 Final decision in relation to famoxadone

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 famoxadone as follows:

Schedule 6 – New Entry

FAMOXADONE.

Index – New Entry

FAMOXADONE

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 famoxadone;

- 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; and (f) any other matters that the Secretary considers necessary to protect public health;
- 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 a new entry for famoxadone 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, famoxadone is a preventative and curative fungicide belonging to the quinone outside inhibitor (QoI) (FRAC group 11[1]) class of fungicides, used in the control of a broad spectrum of plant pathogenic fungi including downy mildew and blights. Famoxadone is likely to play a role in resistance management and expected to offer an additional solution for controlling fungal diseases affecting major crops. Famoxadone is a new technical grade active constituent (TGAC) in Australia and has been approved for many years in a number of countries in the EU and USA.
- In relation to paragraph 52E(1)(c) of the Act, the applicant provided toxicity data about the TGAC and a proposed product.
- The toxicity data indicated that famoxadone is of moderate acute toxicity by the oral route (LD_{50} > 1750 to < 5000 mg/kg bw in rats), which is consistent with the Schedule 6 factors. The substance exhibits low acute toxicity by the dermal (LD_{50} >2000 mg/kg bw in rats) and inhalation (LD_{50} >5300 mg/m^3/4h in rats) routes. It is a slight skin and eye irritant in rabbits, and had a positive reaction in the Buehler skin sensitisation test in guinea pigs. These latter findings are consistent with the Schedule 5 factors of the SPF.
- Repeat-dose, chronic toxicity studies in rats and mice indicated that famoxadone intake caused elevated levels of serum enzymes, indicative of liver damage and liver histopathological effects. Ocular lens cataracts were observed in male and female dogs in sub-chronic and chronic oral studies, beginning at two to three months as evidenced by ophthalmologic examination. The cataracts did not show significant progression over time and dogs did not become clinically blind. Cataracts were not observed in chronic studies in rats and mice, or in a one-year oral study in cynomolgus monkeys. No effects were noted in a Functional Observational Battery (FOB) or with motor activity, in acute and repeat dose neurotoxicity studies in rats. There was no evidence of increased pre- or post-natal

[1] FRAC = Fungicide Resistance Action Committee. https://www.frac.info/frac-teams/working-groups/qol-fungicides/information

quantitative or qualitative susceptibility in rat or rabbit reproduction and developmental studies. Famoxadone was not found to be genotoxic on a weight-of-evidence basis from a battery of in vitro and in vivo studies and was not carcinogenic in mice and rats.

- A concentration-dependent cut-off for famoxadone to a lower schedule or exemption could not be determined from the data provided in the current application.
- An Acceptable Daily Intake (ADI) of 0.006 mg/kg bw/d has been established by the APVMA. No demonstratable adverse effects occurred following a single exposure to famoxadone at doses far exceeding those to which humans would likely be exposed. Overall, the toxicity profile for famoxadone is consistent with a Schedule 6 entry.
- I am satisfied that, for the purposes of paragraph 52E(1)(d) of the Act, the regulator (APVMA) will consider the applicable 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 of dependency, abuse or misuse or diversion into illicit use.
- I also noted for the purposes of paragraph 52E(1)(f) of the Act, that an acceptable daily intake (ADI) for famoxadone of 0.006 mg/kg bw/d has been established based on a No Observed Adverse Effect Level (NOAEL), from ophthalmological and histopathological changes in the lens in a 1-year dietary dog study. An acute reference dose (ARfD) was not considered to be necessary, as no demonstrable adverse effects would be expected to occur following a single exposure to famoxadone in humans.

On the basis of the above considerations and 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 October 2022