Australian Government

Department of Health
Therapeutic Goods Administration

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

Delegate-only final decisions and reasons related to scheduling proposals on agricultural and veterinary chemicals

14 May 2019

Scheduling amendments not referred to expert advisory committee

Subdivision 3D.3 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current *Poisons Standard* and decides not to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZU, that the Secretary decides to make a final decision in relation to the proposed amendment without an interim decision. If the final decision is to amend the current *Poisons Standard*, the Secretary must, in doing so, take into account the matters mentioned in subsection 52E(1) of the Act (including, for example, the risks and benefits of the use of a substance, and the potential for abuse of a substance) and the scheduling guidelines as set out in the *Scheduling Policy Framework for Medicines and Chemicals*.

In accordance with 42ZCZX of the Regulations, the Secretary publishes here the scheduling final decision, the reasons for that decision and the date of effect (for decisions to amend the current *Poisons Standard*, this will be the date when it is expected that the current *Poisons Standard* will be amended to give effect to the decision). These Secretary's final decisions and reasons related to scheduling proposals on agricultural and veterinary chemicals.

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Contents

Part A - Final decisions on matters not referred to an expert advisory committee

1. Delegate-only decisions on agricultural and veterinary chemicals

1.1. Grapiprant

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to grapiprant as follows:

Schedule 4 – New Entry

GRAPIPRANT

Index – New Entry

GRAPIPRANT

Schedule 4

Implementation date: *1 June 2019*

Delegate's considerations

In making this decision, the delegate has considered the following:

- The ***application to amend the current Poisons Standard with respect to grapiprant***;
- The Australian Health Ministers' Advisory Council's ***Scheduling Policy Framework*** (SPF 2018); and
- Section 52E 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

Grapiprant is a NSAID-like veterinary analgesic for the treatment of pain and inflammation associated with osteoarthritis in dogs.

Similar to other NSAIDs currently in use in human and veterinary medicine, this substance demonstrates primarily adverse gastrointestinal effects at high doses, in particular gastrointestinal inflammation, erosion and ulceration. Haematological effects are considered secondary to gastrointestinal blood loss.

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

Grapiprant is a NSAID-like veterinary analgesic for the treatment of pain and inflammation

associated with osteoarthritis in dogs.

(c) the toxicity of a substance:

The acute toxicity of grapiprant and its presentation in a tablet form for oral administration to dogs indicates that it would be expected to have a low acute toxicity profile.

Grapiprant is not considered to be genotoxic and is not expected to pose a carcinogenic risk to humans.

Grapiprant is not considered to be a reproductive or developmental toxicant.

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

Nil.

(e) the potential for abuse of a substance:

Osteoarthritis in dogs will require veterinary diagnosis and management consistent with other Schedule 4 NSAIDs.

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

Grapiprant tablets were approved for use for the treatment of pain and inflammation associated with osteoarthritis in dogs by the US FDA in March 2016 and by the European Medicines Agency in January 2018.

Overall conclusions

After considering all relevant information, the delegate is satisfied that the weight of evidence supports a Schedule 4 entry for grapiprant in the Poisons Standard. Given that (i) the acute toxicity of grapiprant and its presentation in a tablet form for oral administration to dogs indicates that it would be expected to have a low acute toxicity profile; and (ii) osteoarthritis in dogs requires veterinary diagnosis and management, risks associated with the use of grapiprant can be managed by making it a restricted veterinary medicine, similar to other Schedule 4 designated NSAIDs.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new Schedule 4 entry for grapiprant in the Poisons Standard.

The applicant's reasons for the request are:

- Grapiprant is a new, first-in-class, NSAID-like substance (Prostaglandin E2-receptor subtype E4 antagonist) that is currently approved for use in the USA and Europe for the treatment of pain and inflammation associated with osteoarthritis in dogs.
- The APVMA has received an application for the new active constituent (grapiprant) and a set of products (Galliprant) containing 20, 60 or 100 mg grapiprant in tablet form for use in dogs.
- The acute toxicity of grapiprant and its presentation in a tablet form for oral administration to dogs indicates that it would be expected to have a low acute toxicity profile.
- Similar to other NSAIDs currently in use in human and veterinary medicine, this substance demonstrates primarily adverse gastrointestinal effects at high doses (in particular gastrointestinal inflammation, erosion and ulceration). Haematological effects are considered secondary to gastrointestinal blood loss.

- Grapiprant is not considered to be genotoxic and is not expected to pose a carcinogenic risk to humans. Grapiprant is not considered to be a reproductive or developmental toxicant.
- As osteoarthritis in dogs will require veterinary diagnosis and management, and consistent with the Schedule 4 designation for other NSAIDs (e.g. celecoxib, mavocoxib, rofecoxib & valdecoxib) grapiprant should listed under Schedule 4.

Current scheduling status and history

Grapiprant is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Australian regulations

- Grapiprant is not listed on the APVMA Public Chemical Registration Information System (PubCris).
- Grapiprant is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.
- Grapiprant is neither an excipient nor active in any medicines on the ARTG.

International regulations

- [redacted] (grapiprant tablets) were approved for use in the control of pain and inflammation associated with osteoarthritis in dogs by the US FDA, March 2016. NADA 141-455.
- [redacted](grapiprant tablets) was approved for use in the EU for use in the control of pain and inflammation associated with osteoarthritis in dogs by the European Medicines Agency, January 2018.

Substance summary

Grapiprant is a non-steroidal, non-cyclooxygenase inhibiting anti-inflammatory drug in the piprant class. It is a selective antagonist of the prostaglandin E2 EP4 receptor, resulting in a reduction of pain and inflammation.

Table 1: Chemical information for grapiprant

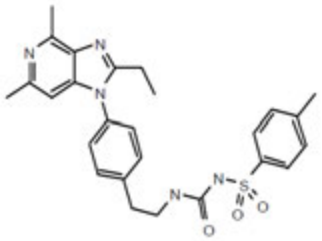
Property	Grapiprant
Chemical structure	
Molecular formula	$C_{26}H_{29}N_5O_3S$
CAS numbers	415903-37-6
IUPAC name	Benzenesulfonamide, N-[[[2-[4-2-ethyl-4-6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl]amino]carbonyl]-4-methylbenzenesulfonamide

Table 2: Acute toxicity end-points for grapiprant

Toxicity	Species	Grapiprant	SPF (2018) Classification[1]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	-	No data	-
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	-	No data	-
Skin irritation	Human, in vitro OECD TG 439	Not a moderate or severely irritant	Not Scheduled
Skin corrosion	Human, in vitro OECD TG 431	Non-corrosive	Not Scheduled
Eye irritation	Bovine, in vitro OECD TG 437	Non-irritating	Not Scheduled
Skin sensitisation (LLNA)	Mouse	Non-sensitising	Not Scheduled

Acute toxicity

Based on the available acute oral toxicity data, grapiprant has a low acute toxicity in rat. While there were no study-specific data on the dermal or inhalational acute toxicity of grapiprant, the substance is presented in Australia as a tablet for veterinary use. As such, the potential for dermal absorption and subsequent dermal toxicity is limited. Further, the form and packaging of the veterinary product ([redacted]) restricts the potential for generation of dust and for inhalation exposure.

Skin irritation

Based on available data, grapiprant is not expected to be a skin irritant:

The EpiDerm Skin Irritation Test (OECD Test Guideline 439) utilises the cellular outcomes of skin irritation (cell death/inflammation) as biomarkers for the potential of chemicals/substances to cause skin irritation of reconstructed human epidermis. Under the conditions of the test, application of grapiprant resulted in a mean relative absorbance of 112% (% of negative control). Based on the cell viability outcome (>50% viability after exposure), grapiprant is not classed as a moderate or severe skin irritant.

The Human Skin Model Test (OECD Test Guideline 431) uses a 3D human skin model (human derived epidermal keratinocytes) and topical application of a test substance, to assess of cell viability and cytotoxicity. Under the conditions of the test, the application of grapiprant resulted in a mean relative absorbance of 91.3 and 102.9% (% of negative control) following 3 minute and 1 hour exposure interval. Based on the cell viability outcome (>50% viability after 3 minute exposure, >15% viability after 1 hour exposure), grapiprant is non-corrosive to skin.

[1] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

Eye irritation

Based on available data, grapiprant is not expected to be irritating to the eyes:

The Bovine Corneal Opacity and Permeability (BCOP) test (OECD Test Guideline 437) uses isolated corneas from the eyes of freshly slaughtered cattle. Grapiprant was applied (20% suspension w/v in saline) to the epithelial surface of the cornea by addition to the anterior chamber of the corneal holder. Damage by the test chemical is assessed by quantitative measurements of: (i) corneal opacity changes, measured as the amount of light transmission through the cornea with the help of an opacitometer; and (ii) permeability, measured as the amount of sodium fluorescein dye that passes from the medium in the anterior chamber of the corneal holder, across the full thickness of the cornea, to the medium in the posterior chamber, detected with the help of a visible light spectrophotometer. Both measurements are used to calculate an In vitro Irritancy Score (IVIS). The calculated mean IVIS for Grapiprant was 2.37. The threshold for classification as severe eye irritant is IVIS ≥55. Grapiprant is therefore not an eye irritant according to the conditions of the test.

Sensitisation

Based on available data, grapiprant is not a skin sensitiser:

A local lymph node assay in mice (OECD Test Guideline 429) was performed using grapiprant at concentrations of 5, 10 and 25% in dimethylformamide (DMF). Two 9-10 week old female mice (BA/CaOlaHsd) were treated by (epidermal) topical application to the dorsal surface of each ear with test item concentrations of 10 and 25% once daily each on three consecutive days. The severity of erythema was assessed and scored. At 25% on day 3 post treatment slight erythema was noted (score = 1). At 10% no signs of erythema were recorded. Five days after the first topical application (day 6) radiolabeled ^{3}H-methyl thymidine (equivalent to 78.9 µCi/mL ^{3}HTdR) were injected into each test and control mouse via the tail vein and euthanized 5 hours later. Draining lymph nodes were rapidly excised and pooled per animal (2 nodes per animal). The ratio of proliferative response of the lymph node cells relative to the lymph nodes of control animals (Stimulation Index; S.I.) was measured and recorded. No symptoms of systemic toxicity were observed during the study period. Slight irritation to the ear skin was observed at 25% on day 3 and 5 but not in animals treated with 5 and 10% grapiprant. Stimulation Indices (S.I.) of 1.95, 2.77 and 2.41 were determined with the test item at concentrations of 5, 10 and 25% in DMF, respectively. A dose response was not observed. The SI in this study are less than 3 thus grapiprant is not considered a skin sensitiser.

Repeat-dose toxicity

In repeat-dose oral (gavage) studies in mice, rats and dogs, the primary target organ was the gastrointestinal tract. In addition, cardiovascular changes were noted in dogs.

In these studies, animals were treated once daily by oral gavage for durations of 10 days to 9 months with grapiprant doses up to 2000 mg/kg bw/d. The main adverse findings were related to gastrointestinal effects, which increased in severity with increasing dose. Cardiovascular effects in dogs were noted at doses higher than 50 mg/kg bw/d. At high doses, changes were observed in clinical chemistry parameters (e.g. decreases total protein, albumin, globulin and calcium) in all species, and in haematological parameters (e.g. decreased red blood cells and haematocrit) in rodents. The haematological effects were considered secondary to the gastrointestinal effects of grapiprant, which at high doses in rodents lead to erosion/ulceration of the gastrointestinal epithelium resulting in blood loss. The NOAEL in mice and rats in 1 month repeat dose oral studies was 100 and 400 mg/kg bw/d, respectively.

In the pivotal 9 month toxicity study in dogs, oral administration of 1, 6 or 50 mg/kg bw/d was associated with mild gastrointestinal clinical signs (e.g. soft-formed faeces, faeces with mucous and occasionally blood present in the faeces) at all dose levels. The frequency of these adverse

effects was dose related. Mild and transient changes in clinical chemistry parameters (e.g. decreased serum albumin & total protein) were mainly seen at the high dose, but were not associated with clinical signs. There were no treatment related effects on liver or kidney function, or gross or histopathological findings of the liver, kidney, stomach or in any coagulation parameters. The NOAEL in dogs in the 9 month repeat dose oral study was 6 mg/kg bw/d due to gastrointestinal effects at 50 mg/kg bw/d.

In other dog toxicity studies, increased heart rate was seen at doses of 100 mg/kg bw/d and higher; and increased QTc intervals were noted at doses of 300 mg/kg bw/d. One death was recorded at 300 mg/kg bw/d.

Genotoxicity

Grapiprant was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays, and based on these studies grapiprant was not considered genotoxic.

Carcinogenicity

No carcinogenicity data were provided, consistent with the APVMA's data guidance for chemicals/substances that are not to be used in food-producing animal species. Moreover, as there was a lack of genotoxic potential and a lack of relevant neoplastic lesions in repeat dose toxicity studies, it was concluded that grapiprant did not pose a carcinogenic risk to humans.

Reproduction and developmental toxicity

In a reproductive toxicity study, rats (25/sex/dose) were administered 0, 100, 300 or 1000 mg/kg bw/d grapiprant in 0.5% methylcellulose (male dosed 4 weeks prior and during mating, females 2 weeks prior to mating until gestation day 7). Males were sacrificed and necropsied 8-9 weeks after start of dosing, and successfully mated females on gestation day (GD 15). There were two deaths (1/sex) in the high dose group that were associated with gastrointestinal tract toxicity. There were no significant effects on body weight, feed consumption, fertility, sperm (concentration, motility or morphology) or reproductive organ weights although clinical signs (gastrointestinal tract distress) were observed. The NOAEL for reproductive toxicity was 1000 mg/kg bw/d, the highest dose tested.

In an embryo-foetal toxicity study, rats (25 females/dose) were administered 0, 100, 300 or 1000 mg/kg bw /d grapiprant in 0.5% methylcellulose vehicle from gestation day (GD) 6 to 15. Animals were sacrificed on GD21. There were no test article-related effects on developmental toxicity, implantation or embryo survival, sex ratio, fetal weight or any other related parameters at the highest dose tested. The NOAEL for maternal toxicity and embryo-fetal toxicity was 1000 mg/kg bw/day, the highest dose tested.

Observation in humans

Trials in humans (three phase 1 trials in health volunteers and one phase 2a in adults with osteoarthritis in the knee) were undertaken as part of a human drug development program. In these studies, grapiprant was administered orally as single dose of 1 to 2000 mg/person or as twice daily doses of 50 to 300 mg/person over a 14 day period. Grapiprant was generally well tolerated and adverse events were mild in intensity and included: abdominal pain, chest pain, nausea and gastrointestinal effects. The incidence of gastrointestinal effects increased with increasing dose following repeated administration of 50 and 250 mg/person twice daily. Serious individual adverse effects were reported after administration of a single oral dose of 1500 mg/person (elevated serum creatinine and blood urea nitrogen) and after administration of repeated doses of 150 mg/person (decreased haemoglobin and haematocrit; and gastrointestinal haemorrhage) (EMA, 2018).

1.2. Spiropidion

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to spiropidion as follows:

Schedule 6 – New entry

SPIROPIDION

Index – New Entry

SPIROPIDION

Schedule 6

Implementation date: *1 June 2019*

Delegate's considerations

- The application to amend the current Poisons Standard with respect to spiropidion;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E 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; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

Spiropidion is a new tetrameric acid derivative insecticide from the group of chemicals that inhibit acetyl co-enzyme (CoA) carboxylase.

Spiropidion is a 'pro-pesticide', being rapidly metabolised to the active form in plants and animals.

In a local lymph node assay (LLNA) test, spiropidion was a skin sensitiser at low concentrations (~0.4%).

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

Spiropidion is a new active constituent for use in agricultural chemical products. However, currently there are no APVMA-approved agricultural chemical products containing spiropidon.

(c) the toxicity of a substance:

Spiropidion has very low acute toxicity by the oral route and low acute toxicity by the dermal route and moderate acute inhalational toxicity. The substance was not a skin or eye irritant but caused a modest degree of skin sensitisation in the local lymph node assay in the mouse.

The new active constituent is not a reproductive or developmental toxin, it is not genotoxic in a battery of *in vivo* and *in vitro* assays and was not carcinogenic in life time studies in mice and rats.

In repeat-dose toxicity studies, there was a treatment-related incidence of adverse clinical signs consistent with being associated with seizures/tremors and/or convulsions in several studies, although the observations were not associated with any gross or histopathological changes. Decreased bodyweights, bodyweight gains and in some cases, food consumption were present at lower doses than associated with the adverse clinical signs and may be attributable to pharmacological toxicity. The adverse clinical signs observed were of sufficient severity to warrant premature sacrifice in the majority of occurrences.

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

Nil.

(e) the potential for abuse of a substance:

Nil.

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

The related tetramic acid compound, spirotetramat, which is approved by the APVMA for use as a commercial insecticide in cotton and in certain fruit and vegetable crops, is in Schedule 6, with no exemption cut-off. Spiropidion and spirotetramat belong to the same chemical class of insecticides (tetramic acids, cyclic ketoenoles) that act as acetyl CoA carboxylase inhibitors.

Overall conclusions

Having considered all the relevant information regarding spiropidion's acute toxicity and skin sensitisation properties and in particular its potential for neurotoxic effects after very short term dosing (seen in the dog), the delegate is satisfied that the potential risks associated with its use warrants spiropidion's inclusion in Schedule 6 of the Poisons Standard.

Following the potential approval of the spiropidion as an active constituent, it is likely that applications will be submitted to register new agricultural products containing the substance. As there is currently no available data on such potential products, especially regarding their composition and uses; and the likely subsequent exposure and relative health risk to workers and the public, there is currently no ground to support exemptions or cut-offs for the Schedule 6 entry.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new Schedule 6 entry for spiropidion in the Poisons Standard.

The applicant's reasons for the proposal are:

- Spiropidion's moderate acute inhalational toxicity.
- In an LLNA test, spiropidion was a skin sensitiser at low concentration (~0.4%).
- Acute and repeat dose toxicity studies revealed severe neurotoxic effects related to the administration of spiropidion in mice, rats and dogs.
- The related compound spirotetramat is in Schedule 6, with no exemption cut-off.
- Following the potential approval of the active ingredient spiropidion, it is likely that applications will be submitted to register new agricultural products containing spiropidion.

As there is currently no available data on such potential products, especially regarding their composition and uses; and the likely subsequent exposure and relative health risk to workers and the public, there is currently no ground to support exemptions or cut-offs to the proposed active ingredient scheduling.

Current scheduling status and history

Spiropidion is a new substance that has not previously been considered for scheduling and is not specifically scheduled in the current Poisons Standard.

The related compound spirotetramat (CAS 2013313-25-1) was considered by the National Drugs and Poisons Schedule Committees (meeting #53) in June 2008. The Committee agreed that the toxicological profile of spirotetramat satisfied the requirements of a Schedule 6 entry. Toxicities included effects on lipid synthesis and change in thyroid function and reproductive toxicity, together with the skin sensitisation and eye irritancy.

Spiropidion and spirotetramat belong to the same chemical class of insecticides (tetramic acids, cyclic ketoenoles) that act as acetyl CoA carboxylase inhibitors.

Australian regulations

- Grapiprant is not listed on the APVMA Public Chemical Registration Information System (PubCris)).
- Grapiprant is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.
- Grapiprant is neither an excipient nor active in any medicines on the ARTG.

International regulations

Spiropidion does not appear to have been evaluated by other international pesticides regulatory agencies.

Spiropidion is not listed as an approved active constituent on the USA EPA Pesticide Chemical Database or on Health Canada's Public Registry.

Spiropidion is not a registered substance on the European Chemical Agency (ECHA) database.

Substance summary

Spiropidion ([redacted]) is a new tetrameric acid derivative insecticide from the group of chemicals that inhibit acetyl CoA carboxylase. Spiropidion is the 'pro'-insecticide, being metabolised to the active form [redacted] rapidly in plants and animals.

Table 1: Chemical information for spiropidion

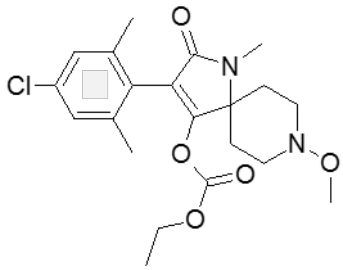
Property	Spiropidion
Chemical structure	
Molecular formula	$C_{21}H_{27}ClN_2O_5$
CAS name	3-(4-chloro-2,6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate
CAS number	1229023-00-0

Table 2: Acute toxicity end-points for spiropidion

Toxicity	Species	Spiropidion	SPF (2018) Classification[2]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	~2670	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000 (no deaths)	-
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>1120 (no deaths)	Schedule 6
Skin irritation	Rabbit	Non-irritant	-
Eye irritation	Rabbit	Non-irritant	-
Skin sensitisation (LLNA)	Mouse	Sensitiser (EC_3 ~0.4%)*	Schedule 6

*Note This value could not be found in the assessment report

Acute toxicity

In rat studies, spiropidion had low acute oral and acute dermal toxicity, and moderate acute inhalational toxicity.

Skin irritation

Spiropidion was not a skin irritant in rabbit studies.

[2] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

Eye irritation

Spiropidion was not an eye irritant in rabbit studies.

Sensitization

Spiropidion was a skin sensitiser in mouse LLNA test (estimated EC_3~0.4%).

Repeat-dose toxicity

Spiropidion was tested in short-term repeat-dose toxicity studies when administered in the diet to mice and rats and in dogs when administered by oral capsule. Long-term dietary toxicity/carcinogenicity studies were performed in mice and rats. The more common effects included decreased bodyweight, bodyweight gain and food intake, and slight to moderate changes in cholesterol and triglycerides.

The more marked observations were severe adverse clinical signs of systemic neurotoxicity in the form of seizures, tremors or convulsions (and associated clinical signs) that were considered to be treatment-related and the severity of these, warranted unscheduled sacrifice. There were no findings at necropsy or at microscopic examination related to these observations. Spiropidion did not cause any dose-dependent treatment-related effects on in-cage, in-hand, arena reactivity and motor activity observations in an acute neurotoxicity study in rats. Repeat-dose neurotoxicity or developmental neurotoxicity studies were not available.

Dogs appeared more sensitive than mice and rats to spiropidion's neurotoxic effects, although the difference may be attributable to the route, i.e. oral gavage/capsule in dogs *vs* diet in mice and rats. The lowest NOAEL values based on neurotoxic effects were 117/126 mg/kg bw/d (M/F) in mice, 44 mg/kg bw/d (M&F) in rats and 10 mg/kg bw/d (M&F) in dogs.

The Acute Reference Dose (ARfD) for spiropidion was established at 0.3 mg/kg bw based on a NOAEL of 30 mg/kg bw in a short term oral dosing study in dogs, where clinical signs of neurotoxicity were seen after two days at 100 mg/kg bw/d and after four days at 65 mg/kg bw/d. In a 52 week dog study, a NOAEL of 10 mg/kg bw/d was established, based on neurotoxic effects at the higher dose of 30 mg/kg bw/d.

An acute neurotoxicity NOAEL was established at 150 mg/kg bw in female rats, based on convulsions 8 h after dosing at 500 mg/kg bw.

Genotoxicity

Spiropidion's potential for genotoxicity was investigated in a standard battery of *in vitro* and *in vivo* tests. All tests were negative except for one *in vitro* test for chromosome aberration in human lymphocytes, which tested spiropidion up to precipitating concentrations, and was positive in the absence and in the presence of metabolic activation. Consideration of all available genotoxicity studies together indicated that overall, spiropidion appeared unlikely to be genotoxic in humans.

Carcinogenicity

Spiropidion was not carcinogenic in life time studies in mice and rats; no treatment-related neoplastic findings were identified in these studies. NOAELs for carcinogenicity were 24 and 18.7 mg/kg bw/d, the highest dose tested in male and female rats, respectively.

Based on a weight of evidence approach considering that an *in vitro* micronucleus test for chromosomal aberration in human lymphocytes, and all *in vivo* genotoxicity studies, including *in vivo* tests for micronucleus damage and chromosomal aberration, were negative; and the absence of carcinogenicity in life-time studies in mice and rats, it was concluded that spiropidion is unlikely to pose a carcinogenic risk to humans.

Reproduction and developmental toxicity

Reproductive toxicity of spiropidion was investigated in a 2 generation study in rats. There were no treatment related effects on reproductive performance, mating behaviour, oestrus cycles, sperm motility, sperm concentration or sperm morphology, fertility, conception, litter sizes, survival, gender ratio or pup development, organ weights or macroscopic examinations. At microscopic examination, an increased incidence of thyroid follicular epithelial cell hypertrophy (minimal) was noted in 9/22 females of both F0 and F1 generations that received the highest dose. This finding was not present at lower doses, nor in males. In the absence of a clear functional deficiency in reproductive performance, the increased incidence was considered to be non-adverse with regard to reproductive toxicity. The NOAEL for reproductive toxicity was the highest dose*, i.e.* 24 and 23 mg/kg bw/d for F0 and F1 generation females, respectively; and 31 and 38 mg/kg bw/d, for F0 and F1 generations males, respectively.

Developmental toxicity studies indicated that spiropidion was not teratogenic in rats and rabbits.

Observation in humans

No data were available.

Public exposure

No data were available. Public exposure estimation is not possible at this stage, as the composition and uses of potential products containing spiropidion that may later be proposed are not known.

Nevertheless, it may be noteworthy that (*i*) submissions to register agricultural products containing spiropidion for the control of sap sucking pests including various insects and mites may be anticipated and (*ii*) spiropidion is a "pro-pesticide", which is rapidly metabolised to the active metabolite in plant and animal tissues.

1.3. 6-Benzyladenine

Delegate's final decision

Final decision:

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to 6-benzyladenine as follows:

Schedule 6 – Amend Entry

6-BENZYLADENINE **except** in preparations containing ~~**2**~~ **10 per cent** or less of 6-benzyladenine.

Index – New Entry

6-BENZYLADENINE

Schedule 6

Delegate's considerations

- The application to amend the current Poisons Standard with respect to 6-benzyladenine
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E 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; and (f) any other matters that the Secretary considers necessary to protect public health.

Implementation date: *1 June 2019*

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

Agricultural products containing 2 per cent 6-benzyladenine are currently approved by the APVMA for use as plant growth regulators.

A proposed new product containing 9.6 per cent 6-benzyladenine is a slight skin and eye irritant. However, it is not a skin sensitiser.

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

A proposed new agricultural chemical product, containing 100 g/L (9.6 %) 6-benzyladenine, is for use in apples. The use profile in apples will be the same as that for a registered product containing 20 g/L (1.9 %) 6-benzyladenine.

(c) the toxicity of a substance:

The submitted data demonstrated that the acute toxicity profile of the product containing 9.8 per cent of 6-benzylademine is not materially different to that of the product containing 2 per cent 6-benzyladenine, which was considered by the Scheduling Committee to establish the

current 2 per cent cut-off level in Poison Standard.

Studies show that it has low acute oral toxicity, low acute dermal toxicity and low inhalation toxicity.

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

Nil.

(e) the potential for abuse of a substance:

Nil.

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

A 6-benzyladenine-containing product containing 9.5 per cent 6-benzyadenine is currently registered in the USA.

Overall conclusions

After consideration of all the relevant information, the delegate is satisfied that the weight of evidence supports that an amendment of the Schedule 6 cut-off concentration level from 2 per cent to 10 per cent is justified. The toxicological data provided supports that the toxicological profile of the product containing 100 g/L (9.6 %) 6-benzyladenine, is not materially different to that of the product containing 20 g/L (1.9 %) 6-benzyladenine and the 100 g/L 6-benzyladenine product will have the same uses as those approved for the 20 g/L product.

On the basis that the proposed changes to the existing entry do not involve down-scheduling or up-scheduling, the delegate is satisfied that the application is not captured as a 'rescheduling' consideration as described in the *Scheduling Handbook, Guidance for amending the Poisons Standard, 2018*.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 6 entry for 6-benzyladenine in the Poisons Standard.

The applicant's reasons for the proposal are:

- Submitted toxicity data for the product containing 9.8% 6-benzyladenine showed a similar hazard profile to an APVMA registered product, containing 2% 6-benzyladenine;
- [redacted] was considered by the NDPSC in 1995 for the purpose of establishing a 2% cut-off for 6-benzyladenine from Schedule 6; and
- The formulation details for [redacted] indicate that the product contains scheduled excipients but they are present at concentrations below their relevant SUSMP cut-off levels.

Current scheduling status

6-Benzyladenine is currently in Schedule 6 of the Poison Standard as follows:

Schedule 6

6-BENZYLADENINE **except** in preparations containing **2 per cent** or less of 6-benzyladenine

Scheduling history

6-Benyladenine was first considered for scheduling by the National Health and Medical Research Council Poison Schedule (Standing) Committee in August 1979. In view of the data submitted at the time by [redacted], the Committee recommended that 6-benzyladenine be exempt from scheduling.

In February 1995 the Committee considered further toxicological data from [redacted] concerning the scheduling of 6-benzyladenine. The Committee considered that despite the moderate acute toxicity (reflecting an S6 classification) the proposed limited use pattern of 6-benzyladenine (i.e.as a plant growth regulator for use on apples) indicated that inclusion in Schedule 5 with an exemption for preparations containing 2% or less was appropriate.

Subsequent to the meeting the Committee was requested to reconsider two critical acute studies in rats; one study gave an LD_{50} of 1380 mg/kg bw whereas a later study gave an LD_{50} of 1290 mg/kg bw. The Chief Toxicologist at the time advised that there was no reason to discriminate between the two rat studies and both should be considered valid. The Committee was also provided with oral acute toxicity data relating to mice studies with an LD_{50} of 1300 mg/kg bw. Following consideration of the additional data, the Committee considered that the acute oral toxicity indicated that Schedule 6 with a 2 per cent cut-off to exemption from scheduling was appropriate.

Australian regulations

- 6-Benzyladenine is an APVMA approved active constituent
- [redacted] (19g/L) and [redacted] (20 g/L) are APVMA registered products
- 6-Benzyladenine is not listed on the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.
- 6-Benzyladenine is not an excipient or active in any medicines on the ARTG.

International regulations

- [redacted] is currently registered (for use in apples and pears) in the USA as [redacted].
- The applicant to the APVMA states applications have been submitted for registration in Austria, Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Portugal and Spain, which are currently under evaluation.

Substance summary

Table 1: Chemical information for 6-Benzyladenine

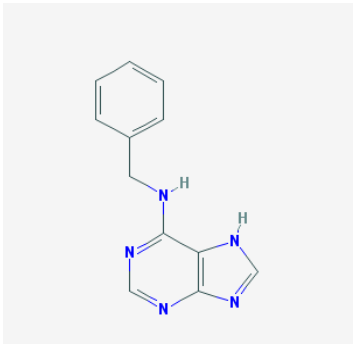
Property	6-BENZYLADENINE
Chemical structure	
Molecular formula	$C_{12}H_{11}N_5$
CAS names	6-benzyladenine
CAS number	1214-39-7
IUPAC and/or common and/or other names	N^6-BENZYLADENINE; N-benzyl-7H-purin-6-amine; 6-BENZYLAMINOPURINE; N-PHENYLMETHYL-1H-PURINE-6-AMINE

Table 2: Acute toxicity end-points for [redacted] (10% 6-benzyladenine) and [redacted] (2% 6-benzyladenine)

Toxicity	Species	End-point (10% product)*	End-point (2% product)**	SPF (2018) Classification[3]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5000 (no deaths)	>5000 (no deaths)	Nil
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2050 (no deaths)	>5000 (no deaths)	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>2060 (no deaths)	>3000 (estimate)	Schedule 5
Skin irritation	Rabbit	Slight irritant	Slight irritant	Schedule 5
Eye irritation	Rabbit	Slight irritant	Slight irritant	Schedule 5
Skin sensitisation	Guinea pig	Negative	Negative	Nil

* [redacted] (APVMA 2018) ** [redacted] (OCS 1995)

[3] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

Studies on the product, [redacted] (9.8% 6-benzyladenine), were provided to APVMA for assessment. The outcome is summarised below.

Acute toxicity

US OCSPP 870-compliant studies in rats with [redacted] (9.8% 6-benzyladenine) show that it has low acute oral toxicity, low acute dermal toxicity, and low inhalation toxicity.

Skin and eye irritation

OECD-compliant studies in rabbits with [redacted] (9.8% 6-benzyladenine) showed it to be a slight skin and eye irritant.

Sensitisation

An OECD guideline-compliant Buehler test in guinea pigs with [redacted] (9.8% 6-benzyladenine) indicated it was not a skin sensitiser.

1.4. Bupivacaine

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to bupivacaine as follows:

Schedule 5 – Amend Entry

BUPIVACAINE in aqueous gel preparations containing 0. 5 per cent or less of bupivacaine, for the dermal spray-on ~~treatment of~~ administration to post-surgical wounds associated with 'mulesing' of sheep; tail docking and castration of lambs; or castration and disbudding/dehorning in calves.

Schedule 4

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

Index

BUPIVACAINE

Schedule 5
Schedule 4

Implementation date: *1 June 2019*

Delegate's considerations

The application to amend the current Poisons Standard with respect to bupivacaine.

- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

The existing Schedule 5 Poisons Standard entry for bupivacaine is specific for aqueous gel preparations containing 0.5 per cent or less of bupivacaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.

However, since the original Schedule 5 entry was implemented, several extensions of use for the product (i.e. extension of use to include tail docking and castration in lambs, and castration and disbudding/dehorning in calves) have been approved by the APVMA.

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

An APVMA-registered aqueous gel product containing 4.2 g/L (0.42 %) bupivacaine (as hydrochloride) is currently approved for use on post-surgical wounds associated with mulesing,

tail docking and castration of lambs and castration and disbudding/dehorning in calves.

(c) the toxicity of a substance:

Bupivacaine has a long history of safety through widespread use in both human therapeutics and veterinary medicines.

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

Nil.

(e) the potential for abuse of a substance:

Concerns about the need for veterinary supervision in dehorning and castration procedures in lambs and calves at later stages in their development are currently covered by the relevant Australian Animal Welfare Standards and Guidelines.[4] These standards provide age-related and developmental stage-related standards and guidance on when a non-veterinarian can and cannot perform such procedures. Further, most states in Australia have strict definitions of when such procedures become a restricted act of veterinary science.

The APVMA will ensure appropriate label directions and label statements that are consistent with the Australian Animal Welfare Standards and Guidelines and other relevant legislation regarding restricted acts of veterinary science.

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

A product containing bupivacaine at 4.2 g/L is registered in New Zealand as a 'Restricted Veterinary Medicine' which is available only under veterinary prescription.

Overall conclusions

The scheduling application is to amend the wording in the Schedule 5 entry to encompass new use patterns approved by the APVMA.

Given that, (i) the exposure profile for these new uses is not significantly greater than the exposure profile for the existing use in mulesing; (ii) bupivacaine has a long history of safe use in human therapeutics and veterinary medicines; and (iii) the rescheduling would be reasonably expected to result in an improvement in animal welfare, with more sheep and cattle being treated to reduced pain and infection, which would otherwise have been left untreated, on balance the delegate is satisfied that the benefits of amending the existing Schedule 5 entry for bupivacaine out-weight the risks. Further, the delegate is satisfied that risks associated with these new uses can be managed by the existing regulatory controls imposed by the Poisons Standard and the APVMA.

On the basis that the proposed changes to the existing entry do not involve down-scheduling or up-scheduling, the delegate is satisfied that the application is not captured as a 'rescheduling' consideration as described in the *Scheduling Handbook, Guidance for amending the Poisons Standard, 2018*.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 5 entry for bupivacaine in the Poisons Standard.

[4] http://www.animalwelfarestandards.net.au/

The applicant's reasons for the proposal are:

- Scheduling application is to amend the wording in the Schedule 5 entry, to encompass additional approved use patterns, i.e. extension of use to include tail docking and castration in lambs, and castration and disbudding/dehorning in calves.
- The product was originally classified as a Schedule 4 prescription medicine. In 2013, a submission was made to the Scheduling Committee by a third party (i.e. not the registrant) to re-schedule the actives to allow the product to be supplied without prescription. The outcome was that new entries in Schedule 5 for both lidocaine and bupivacaine were made, but with wording that aimed to restrict the entry to the specific product/use pattern (i.e. *BUPIVACAINE in aqueous gel preparations containing 0.5 per cent or less of bupivacaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep AND LIDOCAINE in aqueous gel preparations containing 0.5 per cent or less of lidocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep*). Since this time, several extensions of use for the product have been approved by the APVMA. This application therefore aims to update the scheduling entries to reflect the changes in use.

Scheduling history

In November 1977 the National Health and Medical Research Council Poisons Schedule (Standing) Committee considered a proposal to create new Schedule 4 entries for a number of local anaesthetics that included bupivacaine. However, at the August 1983 meeting, it was identified that bupivacaine has been overlooked in the previous evaluation of the scheduling of anaesthetics. The Committee agreed that bupivacaine be listed in Schedule 4 of the Poisons standard with no cut offs.

At the meeting of the Joint Advisory Committee on Medicines and Chemicals Scheduling in March 2013, a proposal was considered which recommended that the Schedule 4 entries for lignocaine, bupivacaine and adrenaline be amended to Schedule 6 when included in a spray-on dermal formulation for direct application to surgical wounds in animals. The primary purpose of the scheduling proposal was to facilitate use as an anaesthetic spray to treat the wounds of sheep during mulesing operation without requiring supply via prescription of a veterinarian.

In the interim decision, the delegate did not support a change to the scheduling of lidocaine or bupivacaine from S4 to S6, considering that 'mulesing' was a procedure that should be carried out under the supervision of a veterinarian.

In the final decision, the delegate set aside the interim decision and enabled scheduling changes that would allow the specific product under consideration to be re-scheduled to S5. This was based on post-decision submissions that indicated veterinary intervention/ supervision was not needed for the proper conduct of 'mulesing' and that use of the product thus far, without veterinary supervision had been working well and with no evidence of inappropriate use. Enabling access without veterinary prescription was also expected to aid farmers and contractors in areas remote from veterinary practice and enable improvements in animal welfare with more sheep expected to be treated to reduce pain and infection.

At the time, a Schedule 6 proposal was not applied as the signal heading POISON was considered inappropriate for veterinary medicines, and the acute toxicity profile for lidocaine (4.06%) and bupivacaine (0.42%) were considered reasonably consistent with the Scheduling Policy Framework guidelines for a listing in Schedule 5. In addition, the product label included appropriate warning statements and safety directions to ensure users were warned of potential risks. It was also noted that lidocaine was available in topical human medicines at up to 10%, with exemption from 2%, for 'over the counter in pharmacies' (Schedule 2). The delegate noted that the re-scheduling should apply only to the particular product and its use in 'mulesing' and in order not to affect other APVMA registered products the following wording was used in the new

Schedule 5 Entry*: BUPIVACAINE in aqueous gel preparations containing 0.5 per cent or less of lidocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.*

Australian regulations

Bupivacaine is not included in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018 for use in listed medicines.

The TGA Ingredient Database identifies that bupivacaine hydrochloride and buvipacaine hydrochloride monohydrate, are available for use as active ingredients in Biologicals, Export Only, Prescription Medicines and as excipients in Biologicals, Devices and Prescription Medicines and as equivalent ingredients in Prescription Medicines.

There are 33 Schedule 4 medicines (all are preparations for injection) currently active on the Australian Register of Therapeutic Goods (ARTG) that contain bupivacaine.

There is currently one APVMA approved veterinary medicine that contains bupivacaine as the active ingredient on PUBCRIS, which is the product for which this scheduling amendment is proposed.

International regulations

- According to the APVMA applicant [redacted] is registered in New Zealand as a Restricted Veterinary Medicine available only under veterinary prescription. However, the use of mulesing is not approved in New Zealand so the pressure driving the original Australian re-scheduling was not present in New Zealand.
- [redacted] is not registered in any other jurisdictions.

Substance summary

Table 1: Chemical information for Bupivacaine

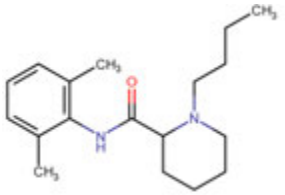
Property	BUPIVACAINE
Chemical structure	 Mol Wt 288.435 g/mol
Molecular formula	$C_{18}H_{28}N_2O$
CAS numbers	2180-92-9
IUPAC and other names	1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide; 1-Butyl-2',6'-pipecoloxylidide

Table 2: Acute toxicity end-points for product: [redacted] containing 40.6 g/L idocaine (as hydrochloride), 4.2 g/L bupivacaine (as hydrochloride), 24.8 mg/L adrenaline (as acid tartrate) and 5.0 g/L cetrimide

Toxicity	Species	Tri-solfen*	SPF (2018) Classification[5]
Acute oral toxicity LD_{50} (mg/kg bw)	rats	Low	S5
Acute dermal toxicity LD_{50} (mg/kg bw)	rats	Low	S5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	-
Skin irritation	N/A	Slight	S5
Eye irritation	N/A	Slight	S5
Skin sensitisation	-	May be a sensitiser	S5

*From original product assessment by APVMA, determined by extrapolation of all actives and excipients in the formulation (under the product name [redacted]).

Based on its use largely as an injectable anaesthetic in humans, there are limited data available as compared with the type of toxicological profile usually available for veterinary medicines. However, bupivacaine has a long history of safety through widespread and frequent use in both human therapeutics and veterinary medicines. The active has been considered by Poison Scheduling previously; therefore minimal detail on the toxicity profile is presented in this application.

Bupivacaine is chemically related to lidocaine and other aminoacyl anaesthetics, sharing an amide linkage between an aromatic group and the amino or piperidine group. Bupivacaine has the same mode of action as lidocaine in electrically excitable tissues. It has been estimated to be about four times more potent and longer lasting than lidocaine in its local anaesthetic effects, and has been used for regional nerve blocks where a prolonged effect is required. For humans, a therapeutic range of bupivacaine has not been firmly established, with plasma concentrations varying dependent upon the amount injected and the site of administration. For example, peak serum concentrations have ranged from 1.06 to 1.25 µg/mL in infants and children, approximately 30 minutes after the administration of bupivacaine (0.5%) 2.5 mg/kg bw by caudal injection. On the other hand, maximum plasma concentrations of 0.22 to 6 µg/mL within 10 to 35 minutes of injection have been reported with the epidural administration of 10 mL of bupivacaine 0.5% in adults, or 1.7 mg/kg in children. Intravenous injection of bupivacaine is not recommended since cardiac arrest has occurred after convulsions from systemic toxicity, presumably a result of unintentional intravascular injection. Furthermore, it has been reported that injection of repeated doses of bupivacaine may cause significant increases in blood concentration with varying degrees of tolerance, but it is generally accepted that plasma concentrations above 4 µg/mL can be related to toxicity[6]. In an early study, iv infusion of a dose of 75 mg bupivacaine salt over 10 minutes to volunteers (mean age 25 years; mean weight 72 kg) resulted in mean arterial plasma concentrations of approximately 5 µg base/mL; no signs of

[5] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

[6] Micromedex (n.d.) Drugdex Drug Evaluations – Bupivacaine.

toxicity were recorded in the volunteers[7]. In six rhesus monkeys, infusion of a mean of 4.4 mg/kg bw (range 2.5-5.7 mg/kg bw) bupivacaine salt resulted in seizures. Plasma concentrations of 2.2-6.2 µg/mL were achieved.

[7] Tucker GT and Mather LE (1975). Pharmacokinetics of local anaesthetic drugs. *Br. J. Anaesth.* **47**, 213-224

1.5. Lidocaine

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to lidocaine as follows:

Schedule 5 – Amend Entry

LIDOCAINE in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on ~~treatment of~~ administration to post-surgical wounds associated with 'mulesing' of sheep; tail docking and castration of lambs; or castration and disbudding/dehorning in calves.

Schedule 4

LIDOCAINE **except**:

a) *when included in Schedules 2 or 5;*

b) *in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or*

Schedule 2

LIDOCAINE in preparations for topical use other than eye drops:

a) *containing 10 per cent or less of total local anaesthetic substances,* ***except*** *in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or*

b) *in divided preparations containing 200 mg or less of total local anaesthetic substances,* ***except*** *in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.*

Index

LIDOCAINE

Schedule 5
Schedule 4
Schedule 2

Implementation date: 1 June 2019

Delegate's considerations

- The application to amend the current Poisons Standard with respect to lidocaine;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

The existing Schedule 5 Poisons Standard entry for lidocaine is specific for aqueous gel preparations containing 0.45 per cent or less of lidocaine for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.

However, since the original Schedule 5 entry was implemented, several extensions of use for the product (i.e. extension of use to include tail docking and castration in lambs, and castration and disbudding/dehorning in calves) have been approved by the APVMA.

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

An APVMA-registered aqueous gel product containing 40.6 g/L (4.06 %) lidocaine (as hydrochloride) is currently approved for use on post-surgical wounds associated with mulesing, tail docking and castration of lambs and castration and disbudding/dehorning in calves.

(c) the toxicity of a substance:

Lidocaine has a long history of safety through widespread use in both human therapeutics and veterinary medicines.

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

Nil.

(e) the potential for abuse of a substance:

Concerns about the need for veterinary supervision in dehorning and castration procedures in lambs and calves at later stages in their development are currently covered by the relevant Australian Animal Welfare Standards and Guidelines.[8] These standards provide age-related and developmental stage-related standards and guidance on when a non-veterinarian can and cannot perform such procedures. Further, most states in Australia have strict definitions of when such procedures become a restricted act of veterinary science.

The APVMA will ensure appropriate label directions and label statements that are consistent with the Australian Animal Welfare Standards and Guidelines and other relevant legislation regarding restricted acts of veterinary science.

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

A product containing lidocaine at 40.6 g/L is registered in New Zealand as a 'Restricted Veterinary Medicine' which is available only under veterinary prescription.

Overall conclusions

The scheduling application is to amend the wording in the Schedule 5 entry to encompass new use patterns approved by the APVMA.

The applicant commented that pain relieving medication being readily available for use in lambs and calves undergoing routine husbandry procedures (such as mulesing, castration, tail docking

[8] http://www.animalwelfarestandards.net.au/

and disbudding/dehorning) has huge potential for animal welfare. As [redacted] is easily administered by lay people as it is a spray preparation, and is currently approved for procedures performed in the field by lay people for the most part, it is considered that its control by Scheduling should be aligned to reflect this use.

Given that, (i) the exposure profile for these new uses is not significantly greater than the exposure profile for the existing use in mulesing; (ii) lidocaine has a long history of safe use in human therapeutics and veterinary medicines; and (iii) the rescheduling would be reasonably expected to result in an improvement in animal welfare, with more sheep and cattle being treated to reduced pain and infection, which would otherwise have been left untreated, on balance the delegate is satisfied that the benefits of amending the existing Schedule 5 entry for lidocaine out-weight the risks. Further, the delegate is satisfied that risks associated with these new uses can be managed by the existing regulatory controls imposed by the Poisons Standard and the APVMA.

On the basis that the proposed changes to the existing entry do not involve down-scheduling or up-scheduling, I am satisfied that the application is not captured as a 'rescheduling' consideration as described in the *Scheduling Handbook, Guidance for amending the Poisons Standard, 2018*.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 5 entry for lidocaine in the Poisons Standard.

The applicant's reasons for the proposal are:

The product [redacted] was originally classified as a Schedule 4 prescription medicine. In 2013, a submission was made to the Scheduling Committee by a third party (i.e. not the registrant) to re-schedule the actives to allow the product to be supplied without prescription. The outcome was that new entries in Schedule 5 for both lidocaine and bupivacaine were made, but with wording that aimed to restrict the entry to the specific product/use pattern (i.e*. LIDOCAINE in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep AND BUPIVACAINE in aqueous gel preparations containing 0.5 per cent or less of bupivacaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep*). Since this time, several extensions of use for the product have been approved by the APVMA. This application therefore aims to update the scheduling entries to reflect the changes in use.

Current scheduling status

Lidocaine is currently listed in Schedules 2, 4 and 5 of the Poison Standard as follows:

Schedule 5

LIDOCAINE in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.

Schedule 4

LIDOCAINE **except**:

a) *when included in Schedules 2 or 5;*

b) *in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or*

c) *in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit.*

Schedule 2

LIDOCAINE in preparations for topical use other than eye drops:

a) *containing 10 per cent or less of total local anaesthetic substances,* ***except*** *in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or*

b) *in divided preparations containing 200 mg or less of total local anaesthetic substances,* ***except*** *in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.*

INDEX

LIDOCAINE

Schedule 5

Schedule 4

Schedule 2

LIGNOCAINE

cross reference: LIDOCAINE

Scheduling history

In February 1998, the NDPSC considered a submission for re-scheduling of dermal preparations containing 1 per cent or less of lignocaine (lidocaine) in packs of 30 g or less from Schedule 2 to unscheduled. Noting that 14 out of 15 products containing ≤ 1% of lignocaine present on the ARTG had 'grandfathered' status for which indications for use were not included on the Register, and considering the adverse reaction profile of the substance, the Committee decided that based on the use pattern at that time, lignocaine should remain a scheduled substance. This decision was affirmed in May 1998 following the Committee's reconsideration of the applicant's comments, and subsequent examination of public comments.

A decision was made by the Committee in February 2001 to amend the Schedule 2 and Schedule 4 entries for lignocaine so that the entries were expressed in terms of local anaesthetic substances. The recommendation from the Trans-Tasman Harmonisation Working Party that 2 per cent lignocaine or less in dermal preparations should be exempted from scheduling was also adopted at this meeting.

In October 2008, the NDPSC considered a proposal to broaden the current Schedule 2 exemption for dermal use (≤ 2 %) to also exempt use on gums. The Committee agreed that given the concerns about the potential for adverse drug reactions (ADRs) at doses only slightly greater than the therapeutic dose range, the use of the substance for the intended indication was not without risk and was therefore not suitable to be made available without any scheduling restriction.

At the meeting of the Joint Advisory Committee on Medicines and Chemicals Scheduling in March 2013, a proposal was considered which recommended that the Schedule 4 entries for lignocaine, bupivacaine and adrenaline be amended to Schedule 6 when included in a spray-on dermal formulation for direct application to surgical wounds in animals. The primary purpose of the scheduling proposal was to facilitate use as an anaesthetic spray to treat the wounds of sheep during mulesing operation without requiring supply via prescription of a veterinarian.

In the interim decision, the delegate did **not** support a change to the scheduling of lidocaine or bupivacaine from S4 to S6, considering that 'mulesing' was a procedure that should be carried out under the supervision of a veterinarian.

In the final decision, the delegate set aside the interim decision and enabled scheduling changes that would allow the specific product under consideration to be re-scheduled to S5. This was based on post-decision submissions that indicated veterinary intervention/ supervision was not needed for the proper conduct of 'mulesing' and that use of the product thus far, without veterinary supervision had been working well and with no evidence of in-appropriate use. Enabling access without veterinary prescription was also expected to aid farmers and contractors in areas remote from veterinary practice and enable improvements in animal welfare with more sheep expected to be treated to reduce pain and infection.

At the time, a Schedule 6 proposal was not applied as the signal heading POISON was considered inappropriate for veterinary medicines, and the acute toxicity profile for lidocaine (4.06%) and bupivacaine (0.42%) were considered reasonably consistent with the Scheduling Policy Framework guidelines for a listing in Schedule 5. In addition, the product label included appropriate warning statements and safety directions to ensure users were warned of potential risks. It was also noted that lidocaine was available in topical human medicines at up to 10%, with exemption from 2%, for 'over the counter in pharmacies' (Schedule 2). The delegate noted that the re-scheduling should apply only to the particular product and its use in 'mulesing.' In order not to affect other APVMA registered products the following wording was used in the new Schedule 5 Entry*: LIDOCAINE in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on treatment of wounds associated with 'mulesing' of sheep.*

Australian regulations

Lidocaine (lignocaine) is an approved active ingredient in both veterinary and human medicines, with a long history of use.

Lidocaine is not permitted to be used in listed medicines, as it is not included in the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.

According to the TGA Ingredient Database, lidocaine (lignocaine) and its hydrochloride are available for use as active ingredients in Biologicals, Export Only, Over the Counter and Prescription Medicines, and as excipients in Biologicals.

There are 172 products containing lidocaine for therapeutic use currently active on the Australian Register of Therapeutic Goods (ARTG). The concentration of lidocaine in these products ranges from 0.5% to 5% and the formulation types include spray (aerosol), ointment, gel, lozenges, dermal patches, medicated dressings, cream, pellets, lotion, liquid, jelly, and injectables.

There are 12 products containing lidocaine registered for animal use on PUBCRIS: four products are for injection (1.7-2%); four products are for dermal application (lotions and creams)and contain lidocaine at 0.5–2% and they all contain at least one other active that is a Schedule 4. Of the two ear drops, lidocaine concentrations are 0.3-0.5%, however only one contains other S4 actives and the other is the only registered lidocaine product for animal treatment without an S4 signal heading. The remaining two products are topical sprays, [redacted] at 4.06% lidocaine, and another for dogs and cats containing 4% lidocaine and a bittering agent. Therefore, the terminology in the amended entry needs to consider the implications for these products.

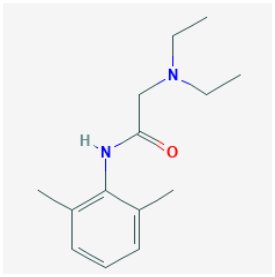
International regulations

According to the applicant, [redacted] is registered in New Zealand as a Restricted Veterinary Medicine available only under veterinary prescription. However, the use of mulesing is not approved in New Zealand so the pressure driving the original Australian re-scheduling was not present in New Zealand.

[redacted] is not registered in any other jurisdictions.

Substance summary

Table 1: Chemical information for lidocaine

Property	LIDOCAINE
Chemical structure	 Mol Wt 234.343 g/mol
Molecular formula	$C_{14}H_{22}N_2O$
INN	Lidocaine (cross-referenced to lignocaine in SUSMP)
CAS number	137-58-6*
EC number	**205-302-8**
IUPAC and/or common and/or other names	IUPAC: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide 2-Diethylamino-2', 6'-acetoxylidide, Numerous other names: xylocaine, lidoderm, lignocainum, solcain, solarcaine etc.

*CAS No. 6108-05-0 is for lignocaine hydrochloride, the active in this product

Table 2: Acute toxicity end-points for lidocaine

Toxicity	Species	Lidocaine	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mice	220 mg/kg bw	S6*
	Rat	317 mg/kg bw	S6*
Acute dermal toxicity LD_{50} (mg/kg bw)	-	No data	-
Acute inhalational toxicity LC_{50} (mg/m^3/4 h)	-	No data	-
Skin irritation	-	Slight	S5
Eye irritation	-	Irritant	S5
Skin sensitisation	Human	Rarely	-

*Previous considerations determined 'POISON' was not an appropriate signal heading for a veterinary medicine and the active, when present in [redacted], was instead classified as a Schedule 5.

Table 3: Acute toxicity end-points for [redacted] containing 40.6 g/L lidocaine (as hydrochloride), 4.2 g/L bupivacaine (as hydrochloride), 24.8 mg/L adrenaline (as acid tartrate) and 5.0 g/L cetrimide

Toxicity	Species	Tri-solfen*	SPF (2018) Classification[9]
Acute oral toxicity LD_{50} (mg/kg bw)	rats	Low	S5
Acute dermal toxicity LD_{50} (mg/kg bw)	rats	Low	S5
Acute inhalational toxicity LC_{50} (mg/m^3/4 h)	N/A	No data	-
Skin irritation	N/A	Slight	S5
Eye irritation	N/A	Slight	S5
Skin sensitisation	-	May be a sensitiser	S5

*From original product assessment by APVMA, determined by extrapolation of all actives and excipients in the formulation (under the product name [redacted]. Registrant: [redacted]

Lidocaine is a water-soluble local anaesthetic. Lidocaine is an aminoethylamide and is a member of the amide class of local anaesthetics. The active is used as a human and veterinary therapeutic for local-regional, epidural, intercostal and topical anaesthetia, and intravenously to treat cardiac arrhythmias (human dose typically 1—10 mg/kg bw).

Lidocaine principally acts as a sodium channel blocker in electrically excitable tissues. In the nervous system it blocks voltage-gated sodium channels at Nodes of Ranvier which, in turn inhibits the propagation of nerve action potentials. As in other excitable tissues, lidocaine selectively blocks sodium channels in their open and inactive states and has little binding capability in the channel resting state. This means that its actions are nerve impulse frequency dependent i.e. its pharmacological actions will increase with an increasing frequency of nerve firing.

Lidocaine's major action on cardiac excitable tissue is as a Class 1b antiarrhythmic agent acting on voltage gated sodium channels. As noted above, its pharmacological actions are frequency dependent and thus lidocaine has little or no effect on slower heart rates and proportionally increasing effects as heart rate increases. Lidocaine decreases the V_{max} in partially depolarised cells with fast response action potentials. The key effects on the cardiac fast-response action potential are to decrease the effective refractory period and to decrease the slope of phase 0 of the action potential curve. These effects decrease arrhythmogenesis during events that cause premature ventricular contractions and ventricular tachycardia[10].

Lidocaine has a long history of safety during widespread and frequent use in both human therapeutics and veterinary medicines. The active has been considered by Poison Scheduling previously, therefore minimal detail on the toxicity profile is presented in this application.

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[9] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

[10] Brunton L.L et al (2018) Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. McGraw-Hill Education

Toxicity

Lidocaine is of moderate toxicity by the oral route (220 mg/kg bw (mice); 317 mg/kg bw (rats) and is expected to be a skin and eye irritant, but not a skin sensitiser[11].

Limited repeat dose studies on lidocaine are available, particularly through routes relevant to occupational exposure. Adverse effects reported in the literature were often a result of mis-use or over use. Lidocaine is readily absorbed orally and from mucus membranes, but poorly absorbed through intact skin. The major adverse effects reported mainly involve the CNS and the cardiovascular system. In humans, the side effects seen with increasing dose include drowsiness, tinnitus, dysgeusia, dizziness and twitching. With increasing dose, seizures, coma and respiratory depression and arrest occur. Cardiovascular depression usually occurs at serum lidocaine levels that product marked CNS effects[12]. In the literature, hypersensitivity reactions have been reported although they are described as rare and mainly related to the ester-type local anaesthetics. The most common adverse findings from topical application appear to be mild skin reactions[13].

The product, [redacted], has previously been assessed to be of low toxicity by the oral and dermal routes, a slight eye and skin irritant and possibly a skin sensitiser. No data were available on the acute inhalational toxicity, however due to their low concentrations in the product and the viscous nature of the formulated product, inhalational exposure and toxicity is likely to be low.

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[11] Mackley, CL (2003) Delayed-type hypersensitivity to lidocaine. Arch Dermatol. 2003;139(3):343-346
[12] EMEA (1999) Committee for veterinary medicinal products: lidocaine summary report. EMEA/MRL/584/99-FINAL, July 1999
[13] HPRA (2016): The Medicines and Healthcare Products Regulatory Agency (UK), Public Assessment Report, Decentralised Procedure, Lignocaine 4% w/w cream

1.6. Sodium salicylate

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is to amend the current Poisons Standard in relation to sodium salicylate as follows:

Schedule 4 – Amend Entry

SODIUM SALICYLATE in preparations for internal use ~~injection~~ for the treatment of animals.

Index

SODIUM SALICYLATE

Schedule 4

Implementation date: *1 June 2019*

Delegate's considerations

- The application to amend the current Poisons Standard with respect to sodium salicylate;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 52E 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

Sodium salicylate is a non-steroidal anti-inflammatory drug (NSAID) used in humans and animals for the treatment of pain and fever. In general, sodium salicylate produces the same adverse reactions as aspirin including stomach ulcers and stomach bleeding.

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

Sodium salicylate is currently approved for use as an injectable veterinary medicine for the treatment of animals. The APVMA has received an application to register a veterinary medicine containing 100% sodium salicylate oral powder.

(c) the toxicity of a substance:

From the available international data and an international assessment report, sodium salicylate has a low to moderate acute oral toxicity, and low acute dermal toxicity. It is not likely to be an inhalation hazard given its very low vapour pressure. It is a moderate eye irritant but not a skin irritant or sensitiser.

Moderate to severe salicylate intoxication leads to adverse effects on the central nervous system, the primary effect of acute salicylate intoxication and the major concern in relation to accidental

poisoning. High doses in rats and dogs results in liver and kidney damage.

Salicylates are not considered genotoxic or carcinogenic. High systemic exposures to salicylates are associated with reproductive, developmental and teratogenic effects.

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

Nil.

(e) the potential for abuse of a substance:

The appropriate use of sodium salicylate in animal treatment would require veterinary diagnosis and oversight. This supports consideration for listing in Schedule 4.

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

Sodium salicylate as an oral veterinary medicine for internal animal treatment (symptomatic treatment of fever and inflammation) is approved for use in the Europe as a prescription medicine. Similar products in the United States (US) are over the counter animal drugs.

Overall conclusions:

After consideration of all the available information, I am satisfied that on balance, the benefits of amending the wording of the current Schedule 4 entry for sodium salicylate to encompass all forms of internal treatments out-weigh the risks. The appropriate use of sodium salicylate in animal treatment would require veterinary diagnosis and oversight, thus supporting a Schedule 4 entry. Therefore, risks associated with the use of new sodium salicylate oral treatments can be managed by the existing regulatory controls imposed by the Poisons Standard.

On the basis that the proposed changes to the existing entry do not involve down-scheduling or up-scheduling, I am satisfied that the application is not captured as a 'rescheduling' consideration as described in the *Scheduling Handbook, Guidance for amending the Poisons Standard, 2018*.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 4 entry for sodium salicylate in the Poisons Standard.

The applicant's reasons for the proposal are:

- A 100% sodium salicylate oral powder product has been proposed to the APVMA for the internal treatment of animals. Sodium salicylate is an APVMA approved active constituent.
- The available toxicological data for sodium salicylate are considered to be sufficient for the purposes of recommending a scheduling decision.
- From the available international data and an international assessment report, sodium salicylate has a low to moderate acute oral toxicity, and low acute dermal toxicity. It is not likely to be an inhalation hazard given its very low vapour pressure. It is a moderate eye irritant but not a skin irritant or sensitiser. Moderate to severe salicylate intoxication leads to adverse effects on the central nervous system, the primary effect of acute salicylate intoxication and the major concern in relation to accidental poisoning. High doses in rats and dogs results in liver and kidney damage. Salicylates are not considered genotoxic or carcinogenic. High systemic exposures to salicylates are associated with reproductive, developmental and teratogenic effects.
- The appropriate use of sodium salicylate in animal treatment would require veterinary diagnosis and oversight. This supports consideration for listing in Schedule 4.

Current scheduling status

Sodium salicylate is currently listed in Schedule 4 of the Poison Standard as follows:

> **Schedule 4**
>
> SODIUM SALICYLATE in preparations for injection for the treatment of animals.
>
> **Index**
>
> **SODIUM SALICYLATE**
>
> Schedule 4

Scheduling history

Sodium sa*l*icylate

In November of 1998, the National Drugs and Poisons Schedule Committee (NDPSC) decided to include sodium salicylate in Schedule 4 in preparations for injection for the treatment of animals, as sodium salicylate would be expected to have a similar toxicity profile to that of aspirin (Schedule 4 for injection) and that veterinary supervision was needed to ensure appropriate use of the injectable form.

Australian regulations

Sodium salicylate

- Sodium salicylate is an APVMA approved active constituent
- [redacted] (150 g/kg sodium salicylate; powder), indicated for the relief of arthritic pain in horses and dogs, is the only APVMA approved oral veterinary product containing sodium salicylate. Registered pack sizes are 0.5 kg to 10 kg.
- There are four APVMA registered sodium salicylate injectable veterinary medicines (50 to 250 mg/mL sodium salicylate).
- There is one APVMA approved keralytic, keratoplastic, antibacterial, antifungal and antipruritic wash for dogs and cats containing sodium salicylate (35 mg/mL).
- Sodium salicylate is available for use as an active ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines.
- Sodium salicylate is not listed on the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.
- There are two products on the ARTG containing sodium salicylate. One is a topical (mucosal) gel product, intended for local pain relief. It contains ethanol, glycerol, lidocaine (lignocaine), menthol, salicylic acid, sodium salicylate, tannic acid, thymolas active ingredients. This product is captured under Schedule 2. A second grandfathered product is a tonic and cough/cold remedy.
- Reported cosmetics uses in relation to sodium salicylate: preservative, denaturant[14].

[14] https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=138#import

International regulations

Sodium salicylate as an oral veterinary medicine for internal animal treatment (symptomatic treatment of fever and inflammation) is approved for use in Europe as a prescription medicine. Similar products in the USA are OTC Animal Drugs.

Based on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry, salicylic acid is being used at concentrations up to 30% in rinse-off products (peels); this is the highest maximum ingredient use concentration that is being reported for rinse-off products.

Substance summary

Table 1: Chemical information for sodium salicylate

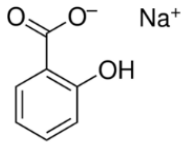
Property	Sodium salicylate
Chemical structure	
Molecular formula	$C_7H_5NaO_3$
CAS name	Sodium salicylate
CAS number	54-21-7
IUPAC name	Sodium;2-hydroxybenzoate

Table 2: Acute toxicity end-points for SODIUM SALICYLATE

Toxicity	Species	Sodium salicylate	SPF (2018) Classification[15]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	300 to 2000	6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	5
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	ND	ND	-
Skin irritation	Rabbit	Non-irritant	-
Eye irritation	Rabbit	Moderate irritant	5
Skin sensitisation (*in vivo*)	Human	Non-sensitising	-

[15] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

Acute toxicity

Studies in rats done according to Organisation for Economic Co-operation and Development (OECD) guidelines show that sodium salicylate has low to moderate acute oral toxicity and low acute dermal toxicity. Sodium salicylate has a low vapour pressure (4.9×10^{-9} Pa at 25°C) and therefore is not predicted to give rise to inhalation toxicity. In humans, it is known that salicylate poisoning in adults can occur at doses of approximately 200 to 300 mg/kg bw, and ingestion of 500 mg/kg bw is potentially lethal. Much lower levels can affect children.

Skin and eye irritation

OECD guideline-compliant studies in rabbits show that sodium salicylate is not a skin irritant but is a moderate eye irritant.

Sensitisation

Sodium salicylate is not considered sensitising to the skin based on a series of studies with up to 31 patients with a history of aspirin intolerance, as well as the lack of any human sensitisation reactions reported in literature concerning dermal exposure to sodium salicylate.

Repeat-dose toxicity, mutagenicity, genotoxicity, carcinogenicity, immunotoxicity, reproduction and developmental toxicity

Once absorbed, sodium salicylate like other salicylates such as aspirin, is metabolised primarily to salicylic acid. Therefore, the toxicological databases applying to salicylates, in particular the larger databases for aspirin and salicylic acid, are relevant to sodium salicylate. The toxicity of these compounds has previously been considered through scheduling.

1.7. Tiafenacil

Delegate's final decision

Final decision

The delegate's final decision under regulation 42ZCZU of the *Therapeutic Goods Regulations 1990* (the Regulations) is not to schedule tiafenacil and to create an Appendix B entry as follows:

Appendix B, Part 3– New Entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
TIAFENACIL	June 2019	a	1

Index – New Entry

TIAFENACIL

Appendix B, Part 3

Proposed implementation date: 1 June 2019

Delegate's considerations

- The application to amend the current Poisons Standard with respect to tiafenacil;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018); and
- Section 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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

Reasons

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

Tiafenacil has a similar mode of action to the approved active constituents, oxyfluorfen, butafenacil, i.e. inhibition of protoporphyrinogen-oxidase (PPO) in plant chloroplasts and interference of haemoglobin synthesis in mammals.

It has a similar acute toxicity to butfenacil and oxyfluorofen, and similarly is neither a developmental nor reproductive toxicant. In addition, tiafenacil shows no evidence of neurotoxicity, immunotoxicity, genotoxicity or carcinogenicity.

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

Tiafenacil is a new agricultural herbicide of the pyrimidinedione chemical class.

(c) the toxicity of a substance:

Based on available data, tiafenacil has low acute toxicity by oral, dermal and inhalational routes

in rats. There were no deaths, clinical signs or macroscopic findings in any of the studies.

While it is a slight eye irritant, tiafenacil is not a skin irritant did not show sensitisation in the maximisation test in guinea pigs or local lymph node assay.

Tiafenacil was not genotoxic in a battery of *in vitro* and *in vivo* assays and was not carcinogenic in life time studies in mice and rats. It is not a reproductive toxin and is not teratogenic though it did show embryo-foetal toxicity in rats at high doses.

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

Nil.

(e) the potential for abuse of a substance:

Tiafenacil has been approved by the APVMA as an active constituent for use as a herbicide. However, there are no agricultural chemical products containing tiafenacil currently registered.

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

Tiafenacil has a similar toxicity profile to butfenacil and oxyfluorofen, and similarly is neither a developmental nor reproductive toxicant and that both butafenacil and oxyfluorfen are both in Appendix B, Part 3 of the SUSMP for agricultural use, due to their low toxicity.

Overall conclusions

Having considered all the relevant information, based on its low toxicity and use as an agricultural chemical product, the delegate is satisfied that tiafenacil does not require control by Scheduling under the Poisons Standard, and should instead be listed in Appendix B, Part 3.

On the basis that the proposed changes to the existing entry do not involve down-scheduling or up-scheduling, the delegate is satisfied that the application is not captured as a 'rescheduling' consideration as described in the *Scheduling Handbook, Guidance for amending the Poisons Standard, 2018*.

Applicant's scheduling proposal and reasons for proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to tiafenacil.

The applicant's reasons for the proposal are:

- Tiafenacil has a similar mode of action to the approved active constituents, oxyfluorfen, butafenacil[16] and saflufenacil[17] i.e. inhibition of protoporphyrinogen-oxidase (PPO) in plant chloroplasts and interference of haemoglobin synthesis in mammals;
- Saflufenacil is in Schedule 5 and 7, based on developmental toxicity seen in rats (but not in rabbits). The only other hazards observed for saflufenacil were slight skin and minimal eye irritation in rabbits;
- Butafenacil and oxyfluorfen have similar acute toxicity profiles to saflufenacil, but are not developmental toxicants. They are both in Appendix B, Part 3 of the SUSMP for agricultural use, due to their low toxicity;

[16] https://apvma.gov.au/sites/default/files/publication/13631-prs-butafenacil.pdf
[17] OCS (2008). Saflufenacil. HRA Technical Report 62853/44119. Department of Health, Canberra, ACT [Previously submitted to NDPSC on 10 March 2008].

- Tiafenacil has a similar acute toxicity to butfenacil and oxyfluorofen, and similarly is neither a developmental nor reproductive toxicant. In addition, tiafenacil shows no evidence of neurotoxicity, immunotoxicity, genotoxicity or carcinogenicity;
- Tiafenacil elicited no effects in a 28-day dermal rat study up to the limit dose (1000 mg/kg bw/d). There were no macroscopic findings of note nor perturbations in clinical chemistry or erythron (haematology/coagulation) parameters;
- An ARfD for tiafenacil was considered unnecessary for the general population (including women of child bearing age), due to tiafenacil's low acute toxicity, lack of neurotoxicity (acute and repeat-dose) and developmental toxicity;
- Based on an assessment of the toxicology of tiafenacil, in particular:
  - Clear NOELS[18] determined in long-term oral studies (in different species) for erythroid effects
  - Clear NOAELS[19] determined in repeat-dose studies in rats for increased liver porphyrin levels (most sensitive marker of toxicity)
  - No effects (including erythroid effects) seen at the limit dose of 1000 mg/kg bw/d in rats in a 28-day dermal study
  - *In vitro* data (in liver mitochondrial fractions) indicating that rodents are significantly more sensitive to PPO inhibition than humans[20]

Current scheduling status and history

Tiafenacil is not currently scheduled, and has not previously been considered for scheduling.

The related substance, butafenacil was placed in Appendix B, Part 3 of the Poisons Standard in May 2000 for the purposes of agricultural use, due to its low toxicity:

APPENDIX B, PART 3 – Substances considered not to require control by scheduling

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
BUTAFENACIL	May 2000	a	1

In June 2009, the NDPSC decided to include the related substance saflufenacil in Schedule 7 due to concerns about developmental toxicity. The NDPSC particularly noted reports that saflufenacil increased skeletal malformations (bent scapula) at a relatively low dose in the absence of any significant signs of maternal toxicity. The NDPSC was concerned with the bent scapula effect, noting that this was an irreversible effect that was a highly unusual developmental toxicity marker. In October 2009 and again in February 2010, following consideration of additional reproductive toxicity data, the NDPSC confirmed the June 2009 Schedule 7 decision. In September 2011, the delegate decided to create an exception from the Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations as follows:

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[18] No Effect Level
[19] No Adverse Effect Level
[20] Fabian E, Niggeweg R & Landsiedel (2008). Study on the inhibition of protoporphyrinogen oxidase (PPO) from rats, mice, rabbits and humans. Experimental Toxicology and Ecology, Agricultural Center Limburgerhof BASF SE 67056 Ludwigshafen, Germany. BASF DocID: 2008/1078593. [Previously submitted to Feb 2010 NDPSC meeting].

Schedule 5 – New entry

SAFLUFENACIL in water dispersible granule preparations.

Schedule 7 – Amendment

SAFLUFENACIL – Amend entry to read:

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

Australian regulations

Tiafenacil is not listed on the APVMA Public Chemical Registration Information System (PubCris).

Tiafenacil not listed on the current Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2018.

Tiafenacil is neither an excipient nor active in any medicines on the ARTG.

International regulations

There are no products containing tiafenacil approved and/or registered in USA, Canada, EU or New Zealand.

Tiafenacil is not listed as an approved active constituent on the USA EPA Pesticide Chemical Database or on Health Canada's Public Registry.

Tiafenacil is not a registered substance on the European Chemical Agency (ECHA) database.

According to the Compendium of Pesticide Common Names (CPCN), the ISO Technical Committee on Common Names for Pesticides has recently approved tiafenacil.

Substance summary

Tiafenacil is a new herbicide of the pyrimidinedione chemical class. Published data on tiafenacil demonstrate that it is a protoporphyrinogen oxidase (ENZYME entry: EC 1.3.3.4) inhibitor (PPO) which causes disruption of chlorophyll synthesis, protoporphyrin IX accumulation and oxidative damage in plants.[21]

[21] Joonghyuk Park, Young Ock Ahn, Jeong-Won Nam, Myoung-Ki Hong, Namsook Song, Taejoon Kim, Gyung-Hee Yu, Soon-Kee Sung. Biochemical and physiological mode of action of tiafenacil, a new protoporphyrinogen IX oxidase-inhibiting herbicide. Pesticide Biochemistry and Physiology. 2018 https://doi.org/10.1016/j.pestbp.2018.08.010

Table 1: Chemical information for Tiafenacil

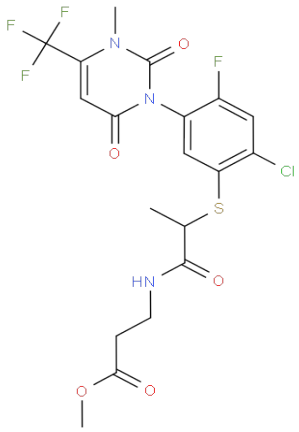
Property	TIAFENACIL
Chemical structure	
Molecular formula	$C_{19}H_{18}ClF_4N_3O_5S$
CAS name	Methyl N-(2-((2-chloro-5-(3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl)-4-fluorophenyl)thio)-1-oxopropyl)-β-alaninateate
CAS number	1220411-29-9
IUPAC and/or common and/or other names	Methyl 3-((2RS)-2-{2-chloro-4-fluoro-5-(1,2,3,6-tetrahydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)pyrimidin-1(6H)-yl) phenylthio}propionamido)propionate

Table 2: Acute toxicity end-points for Tiafenacil

Toxicity	Species	Result	SPF (2018) Classification[22]
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 mg/kg bw with no deaths	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000 mg/kg bw with no deaths	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>5380 mg/m^3 with no deaths	Schedule 5
Skin irritation	Rabbit	Non-irritant	Not scheduled
Eye irritation	Rabbit	Slight, resolving by 72h	Schedule 5

[22] See TGA website for SPF classification guideline – AHMAC – Scheduling policy framework for medicines and chemicals

Toxicity	Species	Result	SPF (2018) Classification[22]
Skin sensitisation (LLNA & GPMT)	Mouse/Guinea pig	Not a sensitiser	Not scheduled

Acute toxicity

Based on the available oral, dermal and inhalation data, tiafenacil has low acute toxicity in the rat. There were no deaths, clinical signs or macroscopic findings in any of the studies.

Skin irritation

Based on available data, tiafenacil is not a skin irritant:

- Three female rabbits received a single (semi-occlusive) topical application of 0.5 g tiafenacil moistened with 0.5 mL reverse-osmosis water for 4 h. Observation for skin irritation was performed at 1, 24, 48 and 72 h after patch removal. Observations for signs of toxicity were made once daily. No dermal reaction was observed in any animal at any time point.

Eye irritation

Based on available data, tiafenacil is a slight eye irritant:

- Three female rabbits were administered 0.1 g tiafenacil (powder) by ocular instillation. The eyes of three rabbits were not washed after treatment. Observation for ocular irritation was performed at 1, 24, 48 and 72 h after instillation. Observations for signs of toxicity were made once daily. In the treated eyes, injection of the conjunctival blood vessels (redness) was evident in all animals at 1 h after instillation, persisting in 2 animals at the 24-h observation, and in 1 animal at the 48 h observation. Very slight discharge was apparent at 1 h after instillation in 1 animal. The treated eyes of all animals were normal at the 72-h examination. No other treatment-related clinical signs were observed during the study. Under the study conditions described, tiafenacil was classified as 'minimally irritating' to the eye. It does not require classification and labelling as an eye irritant according to the European Commission regulation 1272/2008.

Sensitisation

Based on available data, tiafenacil is not a sensitiser in the guinea pig maximisation test (GPMT) or murine local lymph node assay (LLNA):

- In the GPMT, three pairs of intradermal injections were made into the dorsal skin of the scapular region; one group with FCA, another with 15% tiafenacil in PEG 300 and a third group with FCA plus 15% tiafenacil in PEG 300. On Test Day 8, a 2 x 4 cm patch of filter paper was saturated with the test item (~ 0.3 g) at 50% in PEG 300 (or PEG 300 only for the control animals) and placed over the injection sites for 48 h under an occlusive dressing (induction). The reaction sites were assessed for erythema and oedema on a scale of 0-3 according to the method of Magnusson and Kligman at 24 and 48 h after removal of the patches. Test and control animals were challenged 2 weeks after topical induction and treated in the same way as follows: filter paper patches (3 x 3 cm) saturated with the test item at 25% or the vehicle (PEG 300) applied under an occlusive dressing to the left and right flanks, respectively, and left in place for 24 h. The reaction sites were assessed for erythema and oedema at 24 and 48 h after patch removal as noted above. At induction, all control animals had skin reaction scores of 0, while 7 and 3 test animals had scores of 1 (discrete or patchy erythema) at 24 and 48 h, respectively. At 24 and 48 h after topical challenge, all control and all test animals had skin reaction scores of 0 for both flanks. Under the conditions of this study, tiafenacil was not considered to be a skin sensitiser in the GPMT.

- In the murine LLNA, 5 groups of 5 female mice received a topical application of 0 (vehicle control), 10, 25 or 50% tiafenacil in dimethylformamide (DMF), or 25% of the positive control α-hexyl cinnamic aldehyde in DMF, for 3 consecutive days to both ears. Observations for signs of toxicity and local irritation were made once daily. On test day 6 of the assay, mice received in injection of PBS containing [methyl-3H]-thymidine into tail vein and were sacrificed 5-6 h later. Cell proliferation in the draining lymph nodes of the ears of mice from the test substance and positive control groups was then evaluated and compared to the vehicle control group. The stimulation indices (SI) for cell proliferation were 2.2, 2.0 and 2.0 at 10, 25 and 50% tiafenacil, respectively. The positive control (SI = 11.9) confirmed the sensitivity of the assay. Under the study conditions described, tiafenacil was not a skin sensitiser in the LLNA.

Repeat-dose toxicity

In 28-day mouse and rat dietary studies, there were no treatment-related mortalities or clinical signs. Changes in erythroid parameters (reductions in Hb, Hct, RBC, MCH, MCV and MCHC, and increases in RDW) were observed in both sexes at all doses. Liver and spleen weights were increased. In mice, histological findings were observed in the liver (centrilobular hepatocellular hypertrophy). In mice and rats, extramedullary haematopoiesis was seen in spleen at all doses (from 75-90 mg/kg bw/d m/f in both species).

In a 28-day rat dermal study, there was little evidence of systemic toxicity (no mortalities, clinical signs, changes in body weights / organ weights or food consumption, changes in clinical chemistry or in erythroid parameters parameters), although liver focal necrosis was observed in 2/5 females at the highest dose (1000 mg/kg bw/day). There was no evidence of a local irritant effect.

In 90-day mouse and rat dietary studies, there were no mortalities, clinical signs or ophthalmic changes. Reductions in Hb, Hct, MCH and MCV were observed, with increases in reticulocytes, RBC and RDW in both sexes, with significant changes mainly observed at ≥330 ppm (25-28 mg/kg bw/d) in rats and at ≥250 ppm (39-43 mg/kg bw/d) in mice. In both species, spleen weight, splenic enlargement and increased extramedullary haematopoiesis were observed at ≥1100 ppm (84-94 mg/kg bw/d) in rats and ≥250 ppm (39-43 mg/kg bw/d) in mice. Histological findings in the liver were centrilobular hepatocyte vacuolation, single cell hepatocyte necrosis, pigmented Kupffer cells, and mitotic figures in both species, with males being more sensitive than females.

In 90-day and 52-week oral dog studies, there were no mortalities, clinical signs or ophthalmic changes. There were reductions in erythroid parameters (Hb, Hct, MCH, MCV and MCHC) and significantly increased platelet counts, generally significant at 250 mg/kg bw/day in 90-d study and 120 mg/kg bw/day in 52-week study. The main histological findings observed in both studies were pigmented macrophages and extramedullary haematopoiesis in the spleen and increased cellularity of sternal and femoral bone marrow at ≥50 mg/kg bw/day and at 250 mg/kg bw/day in 90-d and 52-week studies, respectively, with increased prothrombin seen in females at > 20 mg/kg bw/d in the latter study.

Genotoxicity

An adequate battery of genotoxicity studies was conducted with tiafenacil. These studies included 3 *in vitro* studies (a point mutation/bacterial reverse mutation assay in Salmonella typhimurium and Escherichia coli strains, a chromosomal aberration assay in human lymphocytes and a mammalian gene mutation study at the Tk locus in mouse lymphoma L5178Y cells) and an *in vivo* study (mouse bone marrow micronucleus test). Studies showed no evidence of a genotoxic potential for tiafenacil.

Carcinogenicity

A 78-week dietary study in mice and a 104-week dietary study in rats, revealed no evidence for carcinogenic potential of tiafenacil.

In the mouse study, there no treatment-related clinical signs or effects on differential leucocyte count or morphology. Liver weight was increased, mainly in males at 75 ppm (8 – 33 m/f), and was associated with abnormal colour and masses, mainly in males at this dose. A number of non-neoplastic lesions in the liver (centrilobular hepatocellular hypertrophy and increased incidences of centrilobular hepatocyte vacuolation, single cell hepatocyte necrosis, pigmented Kupffer cells and foci of clear cell alteration) were observed, mainly in males at 75 ppm, although centrilobular hepatocellular hypertrophy and increased incidence of pigmented Kupffer cells were also observed in males at 10 ppm (1.1 mg/kg bw/d) and centrilobular vacuolation in females at 10 ppm (9.7 mg/kg bw/d). Spleen weights were also increased in males at ≥10 ppm without histological correlates.

In the rat study, there were significant decreases in erythroid parameters (Hb, Hct, RBC, MCH, and MCV) in males at 500 ppm (28 mg/kg bw/d) and females at 1000 ppm (72 mg/kg bw/d). In females at 1000 ppm, there were significant increases in WBC (associated with increases in lymphocytes) and platelets, with similar, but less marked trends in males at 500 ppm. Spleen weights were increased in males at 500 ppm and females at 1000 ppm. This correlated with increased incidences of haematopoiesis in the spleen, mainly females at 1000 ppm. Increased incidences of haematopoiesis were also observed in femoral and sternal bone marrow in females only at 1000 ppm. There were no treatment-related changes in liver weight, but increased incidences of biliary hyperplasia were observed in both sexes (at 500 ppm in males and 1000 ppm in females).

Reproduction and developmental toxicity

In a one-generation reproduction study in rats, reduced erythroid parameters were seen in both sexes at 1000 ppm (69/81 mg/kg bw/day m/f) with more severe effects in males than females. At 100 ppm (6.6/8.5 mg/kg bw/day m/f), there were no treatment related effects, except for significantly increased liver porphyrin concentrations in both sexes. No changes in erythroid parameters were observed at this dose.

In the 2-generation reproduction study in rats, there were no treatment-related mortalities or clinical signs in the F_0 or F_1 parents, with no clear treatment-related haematological changes and no treatment-related clinical chemistry or gross pathological findings, organ weight or histological changes in reproductive organs, pituitary or adrenals. In F_0 or F_1 parents, treatment did not affect reproductive performance (oestrus cycling, mating, fertility, gestation or pregnancy parameters, or the number of live or dead pups delivered nor sperm parameters in males). In F_1 or F_2 pups, there were no treatment-related clinical signs and there was no effect on pup viability indices, body weight gains, gross pathological findings or organ weights (incl. spleen). Liver porphyrin concentrations increased significantly in both sexes in F_0 parents and F_1 weanlings at 150 ppm (6.4-8.6 mg/kg bw/day). There were no changes in erythroid parameters at any dose.

Developmental toxicity studies were carried out in rats and rabbits. In rats, reproductive performance parameters were not affected by treatment, except for a significant reduction in fetal weight at 50 mg/kg bw/day. At this dose, mild maternotoxicity was observed (decreases in MCV (and increases in WBC)). A low incidence of fetuses/litters with an additional liver lobe (within the median cleft) was seen at 50 mg/kg bw/day. It was concluded that none of the observed abnormalities/variants were of toxicological significance. In rabbits, an increased incidence of discolouration of the amniotic sac was observed at 100 mg/kg bw/day but did not affect reproductive performance parameters (including fetal weight). Maternotoxicity (decreased erythroid parameters) was observed at 300 mg/kg bw/day. There was a small reduction in litter incidence of '12 complete ribs' at 100 and 300 mg/kg bw/day. While this

decrease was significant at 300 mg/kg bw/day and outside of the historical control range, so were incidences in the concurrent control group and was therefore not considered to be of toxicological significance.

Available data in rats and rabbits suggest that any embryo/foeto-toxicity in both species occurs at maternotoxic doses and there is no clear evidence for teratogenic potential of tiafenacil in either species.

Observation in humans

No data available

Public exposure

There are no registered products containing tiafenacil in Australia or overseas. Therefore there are no estimates of potential public exposure.