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GENERAL INFORMATION

The *APVMA (Australian Pesticides and Veterinary Medicines Authority) Gazette* is published fortnightly and contains details of the registration of agricultural and veterinary chemicals products and other approvals granted by the APVMA, notices as required by the Agricultural and Veterinary Chemicals Code (the Agvet Code) and related legislation and a range of regulatory material issued by the APVMA.

Pursuant to section 8J(1) of the Agvet Code, the APVMA has decided that it is unnecessary to publish details of applications made for the purpose of notifying minor variations to registration details. The APVMA will however report notifications activity in quarterly statistical reports.

DISTRIBUTION AND SUBSCRIPTION

The *APVMA Gazette* is published in electronic format only and is available from the APVMA website.

If you would like to subscribe to receive email notification when a new edition is published, please complete the subscription form.

APVMA CONTACTS

For enquiries regarding the publishing and distribution of the *APVMA Gazette*: Telephone: +61 2 6770 2300.

For enquiries on the *APVMA Gazette* content, please refer to the individual APVMA contacts listed under each notice.

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Approved Active Constituents

Pursuant to the Agricultural and Veterinary Chemicals Code scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*, the APVMA hereby gives notice that it has approved or varied the relevant particulars or conditions of the approval of the following active constituents, with effect from the dates shown.

1. ACTIVE CONSTITUENT

Application no.:	125999
Active constituent/s:	Amoxicillin trihydrate and potassium clavulanate blend 4:1
Applicant name:	Avet Health Pty Ltd
Applicant ACN:	616 838 101
Summary of use:	For use in veterinary chemical products
Date of approval:	19 February 2021
Approval no.:	89752

Application no.:	126182
Active constituent/s:	S-metolachlor
Applicant name:	Nutrichem Company Limited
Applicant ACN:	N/A
Summary of use:	For use in agricultural chemical products
Date of approval:	23 February 2021
Approval no.:	89819

Application no.:	125100
Active constituent/s:	Iprodione
Applicant name:	Colin Campbell (Chemicals) Pty Ltd
Applicant ACN:	000 045 590
Summary of use:	For use in agricultural chemical products
Date of approval:	24 February 2021
Approval no.:	89507

Application no.:	127273
Active constituent/s:	Metribuzin
Applicant name:	Bharat Rasayan Limited
Applicant ACN:	N/A
Summary of use:	For use in agricultural chemical products
Date of approval:	24 February 2021
Approval no.:	90057

Application no.:	127016
Active constituent/s:	Pyroxsulam
Applicant name:	Corteva Agriscience Australia Pty Ltd
Applicant ACN:	003 771 659
Summary of use:	For use in agricultural chemical products
Date of approval:	24 February 2021
Approval no.:	90007

Application no.:	113107
Active constituent/s:	Oestradiol cypionate
Applicant name:	Syntex SA
Applicant ACN:	N/A
Summary of use:	For use in veterinary chemical products
Date of approval:	24 February 2021
Approval no.:	85381

Application no.:	127010
Active constituent/s:	Cloxacillin sodium
Applicant name:	Zoetis Australia Pty Ltd
Applicant ACN:	156 476 425
Summary of use:	For use in veterinary chemical products
Date of approval:	25 February 2021
Approval no.:	90005

Application no.:	127962
Active constituent/s:	Ivermectin
Applicant name:	Elanco Australasia Pty Ltd
Applicant ACN:	076 745 198
Summary of use:	For use in veterinary chemical products
Date of approval:	26 February 2021
Approval no.:	90196

Application no.:	127291
Active constituent/s:	Detomidine hydrochloride
Applicant name:	Ausrichter Pty Ltd
Applicant ACN:	000 908 529
Summary of use:	For use in veterinary chemical products
Date of approval:	26 February 2021
Approval no.:	90069

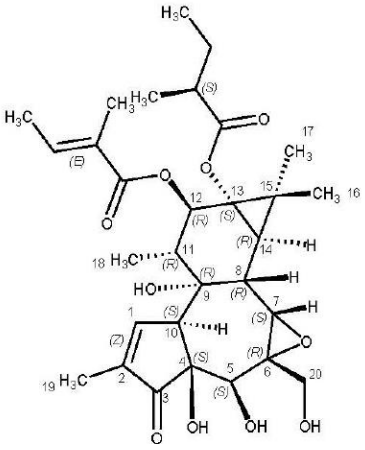
Application no.:	127658
Active constituent/s:	Maduramicin ammonium
Applicant name:	Zoetis Australia Pty Ltd
Applicant ACN:	156 476 425
Summary of use:	For use in veterinary chemical products
Date of approval:	26 February 2021
Approval no.:	90124

Application no.:	127632
Active constituent/s:	Tylosin Tartrate
Applicant name:	Dox-Al Australia Pty Ltd
Applicant ACN:	079 454 265
Summary of use:	For use in veterinary chemical products
Date of approval:	26 February 2021
Approval no.:	90120

New veterinary active constituent and new chemical product STELFONTA containing the active tigilanol tiglate

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application for the approval of a new active constituent tigilanol tiglate, and an application for registration of a new product containing the new active constituent. The product is STELFONTA for use in the treatment of non-metastatic subcutaneous mast cell tumours located at or distal to the elbow or the hock and cutaneous mast cell tumours in dogs.

PARTICULARS OF THE ACTIVE CONSTITUENT

Common name:	Tigilanol tiglate
IUPAC name:	(1a*R*,1b*R*,1c*S*,2a*R*,3*S*,3aS,6a*S*,6b*R*,7*R*,8*R*,8a*S*)-1a,1b,1c,2a,3,3a,4,6a,6b,7,8,8a-dodecahydro-3,3a,6b-trihydroxy-2a-(hydroxymethyl)-1,1,5,7-tetramethyl-8a-[(2*S*)-2-methyl-1-oxobutoxy]-4-oxo-1*H*-cyclopropa[5',6']benz[1',2':7,8]azuleno[5,6-*b*]oxiren-8-yl (2*E*)- 2-methyl-but-2-enoate
Chemical abstracts name:	(1aR,1bR,1cS,2aR,3S,3aS,6aS,6bR,7R,8R,8aS)-1a,1b,1c,2a,3,3a,4,6a,6b,7,8,8a-Dodecahydro-3,3a,6b-trihydroxy-2a-(hydroxymethyl)-1,1,5,7-tetramethyl-8a-[(2S)-2-methyl-1-oxobutoxy]-4-oxo-1H-cyclopropa[5',6']benz[1',2':7,8]azuleno[5,6-b]oxiren-8-yl (2E)-2-methyl-2-butenoate
CAS number:	943001-56-7
Molecular formula:	$C_{30}H_{42}O_{10}$
Molecular weight:	562.65 $gmol^{-1}$
Structure:	
Chemical class:	Phorbol ester
Mode of action:	Activation of protein kinase C

SUMMARY OF THE APVMA'S EVALUATION OF THE ACTIVE CONSTITUENT TIGILANOL TIGLATE IN ACCORDANCE WITH SECTION 5A OF THE AGRICULTURAL AND VETERINARY CHEMICALS CODE (THE 'AGVET CODE'), SCHEDULED TO THE *AGRICULTURAL AND VETERINARY CHEMICALS CODE ACT 1994*

The APVMA has evaluated the chemistry aspects of tigilanol tiglate (identification, physicochemical properties, stability, manufacturing process, quality control procedures, batch analysis results and analytical methods) and found them to be acceptable.

The active constituent, tigilanol tiglate is manufactured to the standard of the manufacturer's specifications.

Impurities of toxicological significance are not expected to occur in tigilanol tiglate as a result of the raw materials and the synthetic route used.

The APVMA has considered the toxicological aspects of tigilanol tiglate, and concluded that there are no toxicological concerns regarding the approval of this active constituent. No acceptable daily intake (ADI) or acute reference dose (ARfD) was established, as tigilanol tiglate is not currently proposed for use in food producing animals.

The Scheduling Delegate for the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons – SUSMP) made a decision to amend the current Poisons Standard to include a new entry for tigilanol tiglate in Schedule 4.

The APVMA is satisfied that the proposed importation and use of tigilanol tiglate would not be an undue toxicological hazard to the safety of people exposed to it during its handling and use.

PARTICULARS OF THE PRODUCT

Proposed product name:	STELFONTA
Applicant company:	QBiotics Group Limited
Name and concentration of active constituent:	1 mg/mL Tigilanol tiglate
Signal heading:	Schedule 4
Summary of proposed use:	For use in the treatment of non-metastatic cutaneous mast cell tumours and subcutaneous mast cell tumours located at or distal to the elbow or the hock in dogs.
Dosage and route of administration:	STELFONTA is provided as a single use vial for intra-tumoral injection. Administer STELFONTA as a single dose of 0.5 mL per cm^3 of tumour volume, as determined on the day of dosing (following initiation of concomitant treatments) by the equations below: Tumour Volume (cm^3) = ½ (length (cm) x width (cm) x height (cm) Dose volume of STELFONTA (mL) to inject = Tumour Volume (cm^3) x 0.5 The maximum dose of STELFONTA is 0.25 mL/kg body weight, with no more than 5 mL (5 mg) administered per dog, regardless of tumour volume or dog body weight. The minimum dose of STELFONTA is 0.1 mL, regardless of tumour volume or dog body weight.
Pack sizes:	2 mL

SUMMARY OF THE APVMA'S EVALUATION OF STELFONTA IN ACCORDANCE WITH THE REQUIREMENTS OF SECTION 14(1)(C) OF THE AGRICULTURAL AND VETERINARY CHEMICALS CODE (THE 'AGVET CODE'), SCHEDULED TO THE *AGRICULTURAL AND VETERINARY CHEMICALS CODE ACT 1994*

1. The APVMA has evaluated the application and in its assessment in relation to whether the safety criteria have been met in accordance with the definition set out in section 5A of the Agvet Code, and proposes to determine that:

(i) The APVMA is satisfied that the proposed use of STELFONTA would not be an undue hazard to the safety of people exposed to it during its handling or use.

The APVMA has conducted a risk assessment for the product and in conjunction with the estimated hazard profile, determined whether the proposed use of the product would not be an undue health hazard to humans, including exposures which may arise from handling the product, or from the accidental injection of the product.

The APVMA has considered the toxicological aspects of STELFONTA from toxicological studies in laboratory animals using the active constituent and the product formulation. Based on the findings of the acute toxicological studies and the active constituent (tigilanol tiglate) and non-actives estimation, the product presents a low acute oral and dermal toxicity, is potentially irritating to the eyes and is a potential skin irritant. The potential for skin sensitisation through dermal exposure is unknown. STELFONTA is presented as an injectable solution and thus is unlikely to present an inhalation hazard.

It is expected that STELFONTA will be administered via intra-tumoral injection by veterinarians only. The greatest risk of exposure to veterinarians is through accidental needle stick/self-injection. Based on toxicological studies adverse effects are considered limited to local inflammatory reactions at the site of self-injection. Pet owners are the other main group at risk of exposure via the dermal route (and secondarily by the oral and ocular routes) through contact with the treated tumour site or contaminated bedding. However as residual levels of tigilanol tiglate at the tumour site were demonstrated to be low, the risk associated with such exposure to pet owners is determined to be low.

Based on the acute and repeat-dose risks associated with STELFONTA, the following first aid instructions are considered appropriate: ‘If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26.’

The proposed safety direction ‘Harmful if swallowed. May irritate the eyes and skin. Avoid contact with eyes and skin. Wear goggles or safety glasses and disposable gloves. Wash hands after use’ will mitigate the oral, dermal and ocular exposure.

The proposed additional user safety statements on the label further mitigate the risks associated with potential self-injection and dermal, ocular and oral exposure to the product. ‘The product is to be administered by a veterinarian only. Accidental self-injection may result in local inflammatory reactions, including swelling, redness and potential wound formation/necrosis, which may take several months to resolve. Caution is required during treatment to avoid self-injection. Dogs undergoing treatment with the product should be adequately restrained, including sedation if necessary. In case of accidental injection, seek medical advice and show the package insert to the physician.

People with known hypersensitivity to tigilanol tiglate or to propylene glycol should avoid contact with the product. The product is an irritant and potentially a skin sensitiser. Accidental exposure to skin, eye or by ingestion should be avoided. Personal protective equipment consisting of disposable impervious gloves and protective eye glasses should be worn when handling the product. If symptoms such as local signs of redness and swelling occur following topical exposure, or if there has been ingestion, seek the advice of a physician and show them the package leaflet.’

(ii) The APVMA is satisfied that the proposed use of STELFONTA will not be an undue hazard to the safety of people using anything containing their residues.

The product is for use in companion animals (dogs) which are non-food producing species and residues are unlikely to enter the food-chain.

(iii) The APVMA is satisfied that the proposed use of STELFONTA is not likely to be harmful to human beings if used according to the product label directions.

The active tigilanol tiglate is listed in Schedule 4 of the Australian Standard for Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-off or exemptions. The Schedule 4 signal heading is PRESCRIPTION ANIMAL REMEDY. The product will be expected to be administered principally by veterinarians.

(iv) The APVMA is satisfied that the proposed use of STELFONTA, would not be likely to have an unintended effect that is harmful to animals, plants or things or the environment.

For veterinary medicinal products (VMPs), the APVMA has adopted VICH guidelines (VICH 2000) on data requirements for environmental safety (amongst other things). It is assumed that VMPs that satisfy the criteria of VICH phase 1 will have limited use and limited environmental exposure and consequently have limited environmental effects.

The APVMA has conducted a VICH Phase I Preliminary assessment to determine the potential for entry of tigilanol tiglate into the environment. STELFONTA will only be used in dogs, which are non-food producing animals. As dogs are not intensively reared and treatments are on an individual basis, environmental exposure is expected to be negligible. The VICH Phase I assessment concluded that the proposed use of STELFONTA will not present a significant risk to the environment.

Disposal instructions are consistent with the Veterinary Labelling Code for the appropriate package size and material will also be included on the label: ‘Dispose of container by wrapping with paper and putting in garbage.’

(v) The APVMA has assessed the target animal safety of STELFONTA from 5 target animal safety studies where the product was administered via intravenous (IV), subcutaneous (SC) and intra-tumoral (IT) routes of administration at single and multiple administrations in dogs. Due to the proposed route of administration being injection into solid mast cell tumours, repeat dose toxicity studies via this route of administration at the therapeutic and above therapeutic doses were not performed. However, a conservative estimate of systemic toxicity was determined through a novel approach of administering the product IV and SC through single and multiple administrations similar to the proposed IT dose rate. Adverse reactions via IV administration included lethargy, distress or excitement with tremors, gait abnormalities, vomiting and thirst. These events resolved without intervention. One death was reported 1 hour after IV administration of a dose of 0.225 mg/kg of STELFONTA. The cause of death was not established but was thought to be related to product administration.

Data from multiple clinical field studies with a total of 306 dogs treated, was also evaluated for safety. The most frequent adverse events observed linked to IT treatment were related to the therapeutic action of the drug, that is local necrosis at the site of injection. Local reactions such as oedema, inflammation and pain were common after injection via IT administration. Most observed adverse events were mild and transient. In the vast majority of cases, these signs were associated with the therapeutic action of the product, were of limited duration and resolved without intervention or with minimal intervention. Four deaths were reported during clinical trials, one was presumed to be related to poor owner compliance of supportive therapy, 2 were related to administration of the product and one was inconclusive. As a result of the reported deaths, the protocols for clinical trials were changed and extra label statements were included.

To mitigate the safety issues for the target animals and advise about adverse effects, the following statements will be included on the label:

- Claims statements are specific for the type, maximum size and location of mast cell tumours.

- A restraint statement to prevent administration of the product via intravenous, intramuscular or subcutaneous injection.
- Precaution statements relating to young animals and breeding, pregnant or lactating animals.
- Precaution statements relating to the provision of supportive treatment and checking for signs of mast cell degranulation reactions by owners.
- Precaution statements relating to care when administration into mucocutaneous locations (eyelid, vulva, preputial opening etc.) and avoiding use of the product near sensitive tissues such as the eyes.
- Side effects statements relating to overdose particularly through IV administration and reported adverse events (very common, common and uncommon).
- Dosage and administration statements relating to the use of recommended concomitant medications in conjunction with the product to reduce adverse effects.

2. The APVMA has evaluated the application and in its assessment in relation to whether the efficacy criteria has been met in accordance with the definition set out in section 5B of the Agvet Code, and proposes to determine that:

(i) The APVMA is satisfied that the proposed use of STELFONTA**,** would be effective when used as directed.

The product, STELFONTA is intended for the treatment of non-metastatic subcutaneous mast cell tumours located at or distal to the elbow or the hock and cutaneous mast cell tumours in dogs. The product is a solution to be administered IT at the recommended dose of 0.5 mg/cm^3 of tumour volume to a maximum dose of 0.25 mg/kg or 5 mg/dog of tigilanol tiglate.

The supporting information included a number of scientific publications, research or clinical efficacy studies in dogs (including pharmacokinetics and pharmacodynamics studies).

Nine clinical field studies (including local) were performed to demonstrate the efficacy of the product. Two of the clinical field studies were conducted using a dose rate of 0.4 mg tigilanol tiglate/cm^3 of tumour volume which is lower than that recommended on the proposed label. The proposed higher dose rate of 0.5 mg tigilanol tiglate/cm^3 of tumour volume was shown to be more effective and did not substantially increase the side effects when compared to the lower dose. The pivotal efficacy study was a blinded, randomised, negative controlled, multi-centre field study to determine if the proposed product was effective in treating dogs with non-metastatic cutaneous and lower limb subcutaneous mast cell tumours. A total of 123 dogs were enrolled in the study and STELFONTA was administered IT to the treatment groups at 0.5 mg tigilanol tiglate/cm^3 of tumour volume. Doses were administered at no less than 0.1 mg and at no greater than 0.25 mg/kg bodyweight up to a maximum of 5 mg/dog in tumours up to 10 cm^3. Efficacy was demonstrated at 0.5 mg/cm^3 of tumour volume. This study also demonstrated that a second treatment administered on day 30, if a complete response is not considered by day 28, can increase the efficacy of treatment.

Follow up studies were conducted for 7 of the efficacy studies to determine the long term prognosis of treatment with STELFONTA. Results indicated that if treatment resulted in a complete response and a dog remains disease free at the injection site for the first 12 months, there is a likelihood it will remain disease free at the injection site for the subsequent 2 to 4 years.

The efficacy studies supported the claim statement: ‘for the treatment of non-metastatic (WHO staging) subcutaneous mast cell tumours located at or distal to the elbow or the hock, and non-metastatic cutaneous mast cell tumours in dogs.’

3. The APVMA has evaluated the application and in its assessment in relation to whether the trade criteria has been met in accordance with the definition set out in section 5C of the Agvet Code, and proposes to determine that:

(ii) The APVMA is satisfied that the proposed use of STELFONTA would not adversely affect trade between Australia and places outside of Australia. The product is for use in dogs, which are not food-producing animals and which do not produce any major Australian export commodities.

MAKING A SUBMISSION

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for approval of the new active tigilanol tiglate should be approved and whether the application for registration of the product STELFONTA should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to approve the active or grant the registration application for the product. These grounds include: for approval of the active constituent, the safety criteria; for the registration application for the product; the safety, efficacy and trade criteria. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA within 28 days of the date of this notice and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

Please note: Submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential (see public submission coversheet).

Please lodge your submission with a public submission coversheet, which provides options for how your submission will be published.

Note that all APVMA documents are subject to the access provisions of the *Freedom of Information Act 1982* and may be required to be released under that Act should a request for access be made.

Please send your written submission and coversheet by email or post to:

Email: enquiries@apvma.gov.au

Post:

Executive Director Risk Assessment Capability

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