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Gazette

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AGRICULTURAL AND VETERINARY CHEMICALS

Australian Government

Australian Pesticides and Veterinary Medicines Authority

The *Agricultural and Veterinary Chemical Code Act 1994* (the Act) commenced on 15 March 1995. The Agricultural and Veterinary Chemicals Code (the Agvet Code) scheduled to the Act requires notices to be published in the *Gazette* containing details of the registration of agricultural and veterinary chemical products and other approvals granted by the Australian Pesticides and Veterinary Medicines Authority. The Agvet Code and related legislation also requires certain other notices to be published in the *Gazette*. A reference to Agvet Codes in this publication is a reference to the Agvet Code in each state and territory jurisdiction.

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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, www.apvma.gov.au/publications/gazette/.

If you would like to receive email notification when a new edition is published, please subscribe on the APVMA website.

APVMA CONTACTS

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

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Erratum Notice

The Australian Pesticides and Veterinary Medicines Authority advises that an error was published in the Commonwealth of Australia Gazette for Agricultural and Veterinary Chemicals, No. APVMA 22, 4 November, 2014.

The Notice of Exemption from Offence Provisions contained a typographical error. The exemption period granted was listed from ‘7 October 2014 to 7 March 2014’ rather than ‘7 October 2014 to 7 March 2015’.

The correct entry for the Exemption from Offence Provisions appears on page 15 of this Gazette.

Imepitoin in the products Pexion 400 mg Tablets for Dogs and Pexion 100 mg Tablets for Dogs

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Boehringer Ingelheim Pty Limited, Vetmedica Division for the approval of a new active constituent imepitoin. The APVMA also has before it applications from the same applicant for the registration of two new products containing the new active constituent. The products are Pexion 400 mg Tablets for Dogs and Pexion 100 mg Tablets for Dogs (the products). The products are an antiepileptic agent for use as an aid in the treatment of epilepsy in dogs.

PARTICULARS OF THE ACTIVE CONSTITUENT

Common Name: Imepitoin

IUPAC Name: 3-(4-chlorophenyl)-5-morpholin-4-yl-4H-imidazol-2-one

CAS Name: 1-(4-Chlorophenyl)-4-(4-morpholino)-1,5-dihydro-1*H*-imidazol-2-one

CAS Registry Number: 188116-07-6

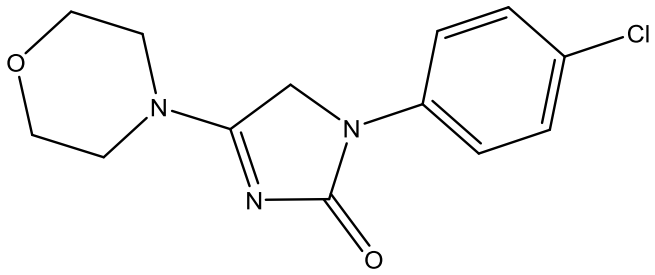
Manufacturer's Codes: ELB 138, E131-00138, AWB 131-138, A-04101, ADD 233089

Minimum Purity: 98.0%-102.0%

Molecular Formula: $C_{13}H_{14}ClN_3O_2$

Molar Mass: 279.73

Structure:



Chemical Family: Imidazolone

Mode of Action: Imepitoin partially activates the GABA receptors, which are responsible for reducing electrical activity between nerve cells. It also has a weak blocking effect on calcium channels that allow electrical signals to be propagated along nerve cells.

SUMMARY OF THE APVMA'S EVALUATION OF IMEPITOIN

Imepitoin is a new active constituent and there is no compendial specification available.

The APVMA has evaluated the chemistry and manufacturing aspects of imepitoin and is satisfied that all the data requirements (including the physico-chemical properties, spectral identification, manufacturing and quality control aspects, impurity formation, active constituent specification, stability, batch analysis data, analytical methods and packaging information) necessary for the approval of this new active constituent have been met.

The Delegate to the Secretary of the Department of Health and Ageing has assessed imepitoin and decided on 3 July 2014 that it be included in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons

(SUSMP) with no cut-off or exceptions. The signal heading that corresponds to Schedule 4 appears on the product labels.

The external toxicology evaluator has indicated that there are no objections on toxicological grounds to the approval of the active constituent imepitoin. Based on the data submitted, imepitoin has low acute oral toxicity. It is not a skin sensitiser, but is a possible slight skin and eye irritant. Imepitoin was not mutagenic or clastogenic in a range of genotoxicity assays. Label statements are required to minimise the risk of irritation. Imepitoin may have reproductive toxicity potential, which is addressed by statements on the product labelling. First Aid Instructions and Safety Directions are required for these products and are included on the product labels.

The APVMA has considered and accepts the findings and recommendations of its advisers. The APVMA is satisfied that the proposed use of imepitoin would not be an undue hazard to the safety of people exposed to it during its handling and use.

PARTICULARS OF THE PRODUCT APPLICATIONS

Proposed Product Name(s):	Pexion 400 mg Tablets for Dogs Pexion 100 mg Tablets for Dogs
Applicant Company:	Boehringer Ingelheim Pty Limited, Vetmedica Division
Name of Active Constituent:	Imepitoin
Signal Heading:	Prescription Animal Remedy - Schedule 4
Summary of Proposed Use:	An antiepileptic agent for use as an aid in the treatment of epilepsy in dogs.
Pack Sizes:	100 tablets, 250 tablets
Withholding Period:	N/A

Summary of the APVMA's evaluation of Pexion 400 mg Tablets for Dogs and Pexion 100 mg Tablets for Dogs in accordance with section 14(3)(e) and (f) 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 applications and in its assessment in relation to human and environmental safety under section 14(3)(e) of the Agvet Code, it proposes to determine that:

   (i) The APVMA is satisfied that the proposed use of the products would not be an undue hazard to the safety of people exposed to them during their handling (section 14(3)(e)(i)).

   An external toxicology evaluator has conducted a risk assessment and found that the submitted data supports the safe use of the products from a toxicological perspective.

   Based on the toxicity profile of the active constituent and those of the product excipients, the products are predicted to be slight skin and eye irritants. No data were submitted on the toxicity of the formulations, therefore the acute toxicity of the products was estimated based on information on the individual components. The products were concluded to have low acute oral toxicity, slight eye and skin irritation potential and no skin sensitisation properties. Although acute dermal and inhalation toxicity could not be determined, these omissions were not critical because the likelihood of significant dermal or inhalation exposure from the tablet formulations is expected to be low.

Exposure of dog owners is possible through hand contact with the product during administration. Apart from possible slight skin and eye irritation no local toxicity is expected and systemic toxicity is unlikely from this route of exposure. Oral exposure may occur as a result of hand to mouth transfer or the accidental direct ingestion of the product by a young child. To mitigate accidental exposure to children, the applicant has proposed that the product be supplied in child resistant packaging. The external evaluator has agreed that this would mitigate the risk of exposure to children.

Based on these findings the external evaluator has recommended that first aid statement (a) (*If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26)* appears on the product labelling. The safety directions '*Wash hands after use.'* will be included on the label, along with the following additional user safety information to minimise the risk of human exposure to the products: '*Harmful if swallowed. May irritate the eyes. Avoid contact with eyes.'*

The APVMA has considered and accepted the findings and recommendations of the external evaluator.

(ii) The APVMA is satisfied that the proposed use of the products will not be an undue hazard to the safety of people using anything containing their residues (section 14(3)(e)(i)).

The products are for use on companion animals only. Imepitoin is unlikely to enter the food chain and therefore the determination of an Acceptable Daily Intake, Acute Reference Dose and Maximum Residue Limits are not considered necessary.

(iii) The APVMA is satisfied that the proposed use of the products containing the active constituent imepitoin is not likely to be harmful to human beings (section 14(3)(e)(ii)) if used according to the product label directions.

The Delegate to the Secretary of the Department of Health for Scheduling made a decision on 3 July 2014 that imepitoin be included in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-off or exceptions. The appropriate Schedule 4 signal heading and the first aid instructions and safety directions will appear on the product label.

2. The APVMA has evaluated the applications and in its assessment in relation to environmental safety under section 14(3)(e)(iii) of the Agvet Code, it proposes to determine that:

(i) The APVMA is satisfied that the proposed use of the products containing the active constituent imepitoin would not be likely to have an unintended effect that is harmful to animals, plants or things or the environment if used according to the product label directions.

The Department of Sustainability, Environment, Water, Population and Communities (DSEWPaC - now the Department of the Environment) has advised that the products meet the criteria for the environmental risk assessment to stop at VICH Phase I (where the potential for environmental exposure is assessed based on the intended use of the product). DSEWPaC have recommended to the APVMA that the use of the products in the proposed manner and with the estimated levels of use is unlikely to have an unintended effect that is harmful to the environment. The APVMA has considered these findings and accepts the recommendations of DSEWPaC. The product labels will contain a suitable disposal statement.

The APVMA has assessed the safety of the the products to target animals based on data submitted to it by the applicant. The margin of safety data supported a 3x safety margin in healthy dogs less than one year of age over a period of six months. The safety margin is based on the maximum label dose rate of 30 mg/kg bodyweight orally twice daily. The efficacy and safety data supports that the applicant formulation has an acceptable safety profile in the target animal (dogs) over the label dose range of 10–30 mg/kg bodyweight orally twice daily.

The APVMA is satisfied that the products would not have an unintended effect that is harmful to animals. Contraindications, precautions and side effects statements will be included on the label.

3. The APVMA has evaluated the applications and in its assessment in relation to whether the trade criterion has been met in accordance with section 14(3)(e)(iv) of the Agvet Code, it proposes to determine that:

   (i) The APVMA is satisfied that the proposed use of the products would not unduly prejudice trade or commerce between Australia and places outside Australia as the products are for use in dogs, which are not food-producing animals nor do they produce any major Australian export commodities.

4. The APVMA has evaluated the applications and in its assessment in relation to whether the efficacy criterion has been met in accordance with section 14(3)(f) of the Agvet Code, it proposes to determine that:

   (i) The APVMA is satisfied that data from trials supporting the efficacy of the products adequately demonstrate that if used according to the product label directions, the products are effective for their proposed uses.

   Dose determination data, pharmacokinetic data and confirmatory field efficacy data were submitted in support of the efficacy of the products**.** The active ingredient, imepitoin, belongs to a new class of antiepileptic drugs that are stated to act as low affinity partial agonists at the benzodiazepine receptor. In the pharmacokinetic study, dogs received the applicant formulation at 30 mg/kg orally twice daily for five days, and were either fed or fasted. The data supports improved absorption when the formulation is administered to fasted dogs at that dose rate. Plasma concentrations of imepitoin fell to the limit of detection within 24 hours after the final dose. Mean pharmacokinetic parameters recorded included a C_{max} in fasted dogs of 17168 ng/mL (T=2.17 hours), compared to a C_{max} of 14892 ng/mL in fed dogs (T=2.02 hours). Other reported mean pharmacokinetic parameters for fasted dogs included AUC_{inf} = 90310 h*ng/mL, V_z = 663 mL/kg and Cl = 320 mL/kg/h. For fed dogs the reported mean parameters were AUC_{inf} = 69238 h*ng/mL, V_z = 1129 mL/kg and Cl = 417 mL/kg/h.

   A pivotal efficacy study demonstrated non-inferiority of the applicant formulation at a dose rate of 10–30 mg/kg bodyweight orally twice daily over 140 days when compared to phenobarbitone at the recommended dose rate. In this study the non-inferiority of imepitoin to phenobarbitone was tested and demonstrated in the per protocol population. *A* reduction was shown in the baseline mean seizure frequency from 2.3 seizures per month in the imepitoin group and from 2.4 seizures per month in the phenobarbitone group to 1.1 seizures per month in both groups after 20 weeks of treatment. The percentage change in monthly seizure frequency was 52.69% for imepitoin and the percentage of responders (proportion of dogs showing at least 50% reduction in monthly seizure frequency compared to baseline) was 75%, though the difference between these values and those for phenobarbitone were not statistically significant.

   Confirmatory field efficacy data supported a responder rate of 75% for the applicant active constituent over the dose range 5–30 mg/kg bodyweight orally twice daily, although there was no statistically significant difference between responder rates when compared to phenobarbitone. The mean seizure frequency decreased by 49.8% compared to baseline in the responders. The addition of the applicant active constituent to the treatment regimens of chronically seizuring dogs refractory to phenobarbitone resulted in 59% responders. The overall reduction in seizure frequency was not statistically significant. The responders however did show a statistically significant ($p<0.05$) mean reduction in seizure frequency of 47.2%. Overall, the data supports the potential for comparative antiepileptic efficacy and superior safety outcomes for the products compared to conventional epilepsy treatment.

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 imepitoin should be approved and whether the applications for registration of the products 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 applications for the products. These grounds include: for approval of the active constituent, the safety and trade criteria. For the registration applications for the products: 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 active constituent should be approved and whether the products should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address
- the date you made the submission.

All personal and *confidential commercial information (CCI)*[1] material contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to approve the active constituent and grant the applications for registration that relate to the grounds for active approval and/or product registration should be addressed in writing to:

Enquiries
Registration Management & Evaluation
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604

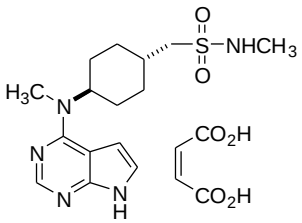
Phone: +61 2 6210 4700
Fax: +61 2 6210 4741
Email: enquiries@apvma.gov.au

[1] A full definition of 'confidential commercial information' is contained in the Agvet Code.

Oclacitinib in the products Apoquel 16 mg, Apoquel 5.4 mg and Apoquel 3.6 mg

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Zoetis Australia Pty Ltd for the approval of a new active constituent oclacitinib. The APVMA also has before it applications from the same applicant for the registration of three new products containing the new active constituent. The products are Apoquel 16 mg, Apoquel 5.4 mg and Apoquel 3.6 mg (the products). The products are to be used for the treatment of pruritus associated with allergic dermatitis in dogs, and for the treatment of the clinical manifestations of atopic dermatitis in dogs.

PARTICULARS OF THE ACTIVE CONSTITUENT

Common Name:	Oclacitinib
IUPAC Name:	*N*-methyl-1-[*trans*-4-(methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino)cyclohexyl]methanesulfonamide (2*Z*)-2-butenedioate
CAS Name:	Cyclohexanemethanesulfonamide, *N*-methyl-4-(methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino)-, trans-(2*Z*)-2-butenedioic acid
CAS Registry Number:	1208319-27-0
Minimum Purity:	96.5%
Molecular Formula:	$C_{15}H_{23}N_5O_2S \cdot C_4H_4O_4$
Molar Mass:	453.5 g/mol
Structure:	
Chemical Family:	pyrrolo-pyrimidine sulphonamide
Mode of Action:	Janus kinase (JAK) receptor inhibitor with activity against JAK-1 and JAK-3

SUMMARY OF THE APVMA'S EVALUATION OF OCLACITINIB

Oclacitinib is a new active constituent and there is no compendial specification available.

The APVMA has evaluated the chemistry and manufacturing aspects of oclacitinib and is satisfied that the criteria (including the physico-chemical properties, spectral identification, manufacturing and quality control aspects, impurity formation, active constituent specification, stability, batch analysis data, analytical methods and packaging information) necessary for the approval of this new active constituent have been met.

The Delegate to the Secretary of the Department of Health for Scheduling has assessed oclacitinib and decided on 28 October 2014 that oclacitinib be included in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-offs or exceptions, with an implementation date of 1 February 2015.

The Office of Chemical Safety (OCS) has indicated there are no objections on toxicological grounds to the approval of the active constituent oclacitinib. Based on the data submitted, oclacitinib is a moderate acute oral toxicant and a low

acute dermal toxicant. It is not a skin irritant, and is a non-sensitiser at concentrations ≤ 4%. Oclacitinib was a severe eye irritant. Since the formulated product is a film-coated tablet it would not be expected to generate fine material of inhalational risk in this case, therefore an acute inhalational toxicity study was not considered necessary. Oclacitinib was not a developmental toxicant in rat or rabbit. It is not genotoxic in *in vitro* and *in vivo* assays.

The APVMA has accepted the findings and recommendations of its advisers. The APVMA is satisfied that the proposed use of oclacitinib would not be an undue hazard to the safety of people exposed to it during its handling and use.

PARTICULARS OF THE PRODUCT APPLICATIONS

Proposed Product Name(s):	Apoquel 16 mg Apoquel 5.4 mg Apoquel 3.6 mg
Applicant Company:	Zoetis Australia Pty Ltd
Name of Active Constituent:	Oclacitinib
Signal Heading:	Prescription Animal Remedy - Schedule 4
Summary of Proposed Use:	For the treatment of pruritus associated with allergic dermatitis in dogs. For the treatment of the clinical manifestations of atopic dermatitis in dogs.
Pack Sizes:	20 tablets, 100 tablets (bottle) 20 tablets, 100 tablets (blister pack)
Withholding Period:	N/A

SUMMARY OF THE APVMA'S EVALUATION OF APOQUEL 16 MG, APOQUEL 5.4 MG AND APOQUEL 3.6 MG IN ACCORDANCE WITH SECTION 14(3)(E) AND (F) OF THE AGRICULTURAL AND VETERINARY CHEMICALS CODE (THE 'AGVET CODE'), SCHEDULED TO THE *AGRICULTURAL AND VETERINARY CHEMICALS CODE ACT 1994*

5. The APVMA has evaluated the applications and in its assessment in relation to human and environmental safety under section 14(3)(e) of the Agvet Code, it proposes to determine that:

   (iv) The APVMA is satisfied that the proposed use of the products would not be an undue hazard to the safety of people exposed to them during their handling (section 14(3)(e)(i)).

   The Office of Chemical Safety (OCS) in the Department of Health has conducted a risk assessment and found that the submitted data supports the safe use of the products from a toxicological perspective.

   A toxicity estimation for the proposed products suggests that the products are likely to be low acute oral and dermal toxicants, non-irritating and non-sensitising to skin, and have moderate eye irritation potential. The OCS considers that the nature of the product formulation (as film-coated tablet) is not expected to produce sufficient residue to pose unacceptable eye irritation risks to domestic users, even if tablets are broken for administration. Risks associated with acute hazards and accidental ingestion by children may be mitigated by label statements and appropriate safety direction hazard/precautionary statements, noting that the products will be supplied in child-resistant packaging.

   Based on these findings the OCS has recommended that first aid statement (a) (*If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26)* appear on the product labelling along with the

following safety directions: *Will irritate the eyes. Avoid contact with eyes. Wash hands after use.* The OCS has also recommended that a precautionary statement be included as follows: *Accidental ingestion of oclacitinib can be harmful for children. To avoid accidental ingestion, administer the tablet to the dog immediately after removal from the package. Keep out of reach and sight of children.*

The APVMA has considered and accepted the findings and recommendations of the OCS evaluation.

(v) The APVMA is satisfied that the proposed use of the products will not be an undue hazard to the safety of people using anything containing their residues (section 14(3)(e)(i)).

The products are for use on companion animals only. Oclacitinib is unlikely to enter the food chain and therefore the determination of an Acceptable Daily Intake, Acute Reference Dose and Maximum Residue Limits are not considered necessary.

(vi) The APVMA is satisfied that the proposed use of the products containing the active constituent oclacitinib is not likely to be harmful to human beings (section 14(3)(e)(ii)) if used according to the product label directions.

The Delegate to the Secretary of the Department of Health for Scheduling has assessed oclacitinib and decided on 28 October 2014 that oclacitinib be included in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) with no cut-offs or exceptions, with an implementation date of 1 February 2015. The appropriate signal heading and the first aid instructions, safety directions and precautionary statement recommended by the OCS will appear on the product label.

6. The APVMA has evaluated the applications and in its assessment in relation to environmental safety under section 14(3)(e)(iii) of the Agvet Code, it proposes to determine that:

(ii) The APVMA is satisfied that the proposed use of the products containing the active constituent oclacitinib would not be likely to have an unintended effect that is harmful to animals, plants or things or the environment if used according to the product label directions.

The Department of the Environment has advised that the products meet the criteria for the environmental risk assessment to stop at VICH Phase I (where the potential for environmental exposure is assessed based on the intended use of the product). The Department of the Environment has recommended to the APVMA that the use of the products in the proposed manner and with the estimated levels of use is unlikely to have an unintended effect that is harmful to the environment. The APVMA has considered these findings and accepts the recommendations of the Department of the Environment. The product labels will contain a suitable disposal statement.

The APVMA has assessed the safety of the products to target animals based on data submitted to it by the applicant. Margin of safety studies were conducted which demonstrated that the active constituent (as the citrate salt) had a margin of safety of 1.9x for treatment over 90 days in 8 month old beagle dogs, and a margin of safety of 7.5x for treatment over 28 days in 12 month old beagle dogs. Duration of treatment studies show that the proposed formulation has a safety margin of 4.5x for the proposed regimen and of 3x over the studied duration of use (26 weeks). A study in 5–6 month old beagle dogs revealed a narrow margin of safety (1–1.5x) and for this reason the use of the proposed product in this age group (dogs less than 12 months of age) is not recommended, and this will be included on the label. The target animal safety studies are based on the proposed label dose regimen of 0.4 mg/kg bodyweight, up to a maximum of 0.6 mg/kg bodyweight, administered orally twice daily for 14 days, and then administered once daily for maintenance therapy.

The APVMA is satisfied that the products would not have an unintended effect that is harmful to animals. The contraindications, precautions and side effects that were identified in the submitted data are not considered to

preclude the safe use (according to the label instructions) of the products in the target animal. The contraindications, precautions and side effects will be included on the label.

7. The APVMA has evaluated the applications and in its assessment in relation to whether the trade criterion has been met in accordance with section 14(3)(e)(iv) of the Agvet Code, it proposes to determine that:

   (ii) The APVMA is satisfied that the proposed use of the products would not unduly prejudice trade or commerce between Australia and places outside Australia as the products are for use in dogs, which are not food-producing animals nor do they produce any major Australian export commodities.

8. The APVMA has evaluated the applications and in its assessment in relation to whether the efficacy criterion has been met in accordance with section 14(3)(f) of the Agvet Code, it proposes to determine that:

   (ii) The APVMA is satisfied that data from trials supporting the efficacy of the products adequately demonstrate that if used according to the product label directions, the products are effective for their proposed uses.

   Dose determination studies, dose confirmation studies, pharmacodynamic and pharmacokinetic studies, laboratory model efficacy studies and confirmatory field efficacy studies were submitted in support of the efficacy of the the products. The pharmacodynamics data support the claim that the active constituent is a selective Janus kinase 1 (JAK1) inhibitor that also inhibits JAK1/3 dependent cytokines important in the pathophysiology of canine atopic dermatitis. The pharmacokinetic study showed that dogs receiving 0.5mg/kg bodyweight oclacitinib citrate orally twice daily for seven days had a mean C_{max} = 415 ng/mL (T=0d), 620 ng/mL (T=1d) and 585 ng/mL (T=6d), and mean T_{max} = 0.6–0.9h. Mean trough plasma concentrations were in the range 99.0–185 ng/mL. Near steady state plasma concentrations were achieved within 24 hours. T—cell inhibition was maximal at 1–2 hours post dose, following a similar curve to the oclacitinib plasma concentration curve. There was no evidence of hysteresis in the concentration-effect plots and a simple E_{max} model adequately described the pharmacokinetic—pharmacodynamic relationship.

   The confirmatory field/clinical studies support the safety and efficacy of a regimen of 0.4 mg/kg bodyweight oclacitinib maleate orally twice daily for fourteen days followed by 0.4 mg/kg bodyweight orally once daily for ninety-eight days, as the most appropriate of the regimens tested for the treatment of clinical atopic dermatitis. Mean decreases of 68–74% in owner assessed Visual Analogue Scale (VAS) score and 67–71% in vet assessed Canine Atopic Dermatitis Extent and Severity Index (CADESI-02) scores were reported. The data from the clinical trials support the claim *for the treatment of pruritus associated with allergic dermatitis in dogs, and for the treatment of the clinical manifestations of atopic dermatitis in dogs.*

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 oclacitinib should be approved and/or whether the applications for registration of the products 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 constituent and grant the registration applications for the products. These grounds include: for approval of the active constituent, the safety and trade criteria. For the registration applications for the products: 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 active constituent should be approved and whether the products should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or group name (if relevant)
- email or postal address
- the date you made the submission.

All personal and ***confidential commercial information (CCI)***[2] material contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to approve the active constituent and/or grant the applications for registration that relate to the grounds for active approval and/or product registration should be addressed in writing to:

Enquiries
Registration Management and Enquiries
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604

Phone: +61 2 6210 4700
Fax: +61 2 6210 4741
Email: enquiries@apvma.gov.au

[2] A full definition of 'confidential commercial information' is contained in the Agvet Code.

Cancellation of Registration at the Request of the Holder

At the request of the holder, the APVMA has cancelled the registration and the associated label approval of the following product:

Product no.	Product name	Approval holder	Date of effect
62639	RACS FENAMIPHOS 400 NEMATICIDE AND INSECTICIDE	RURAL AGRICULTURAL CHEMICAL SUPPLIERS PTY LTD	7 November 2014

The following instructions set out how a person can deal with the cancelled product.

SUPPLY

A person may supply or cause to be supplied product manufactured prior to 7 November 2014 at wholesale and retail level, until the 7 November 2015.

After 7 November 2015 it will be an offence against the Agvet Codes to have possession or custody of the product with the intention to supply, or to supply the product.

USE

A person may continue to use the product according to its label instructions until 7 November 2015.

Any person who possesses, has custody of, uses, or otherwise deals with the listed product in accordance with the above instructions is taken to have been issued with a permit under the Agvet Codes to so possess, have custody of, use or otherwise deal with the product after the registration has been cancelled until 7 November 2015.

The supply and use of the product must be in accordance with the conditions of registration, including any conditions relating to the shelf life or expiry date.

It is an offence to possess, have custody of, use, or deal with the product listed in the table in a manner that contravenes the above instructions.

APVMA CONTACT

For any enquiries or further information about this matter, please contact:

Chemical Review
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
SYMONSTON ACT 2609

Phone: +61 2 6210 4749
Fax: +61 2 6210 4776
Email: chemicalreview@apvma.gov.au

Exemption from Offence Provisions

EXMEPTION FOR THE PURPOSES OF SECTION 75 AND SECTION 78

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has determined, as provided for under sections 75(1)(b) and 78(1)(b) of the Schedule to the *Agricultural and Veterinary Chemical Code Act 1994* (the Agvet Code), that the products listed below are exempt from the operation of section 75 and section 78 of the Agvet Code.

PRODUCTS SUBJECT TO THIS EXEMPTION

1. Zagrosol AD3E (oral solution)

2. Amilyte (water soluble powder)

3. Nilstress (water soluble powder)

4. Zagrosol Minpro (oral solution)

5. Zagrosol Aminogen (oral solution)

6. Calpozag (oral solution)

This exemption is granted for the period of 7 October 2014 to 7 March 2015 inclusive.

While in force this exemption means that while the products are veterinary chemicals, as defined by section 5 of the Agvet Code, and unregistered, it is not an offence to possess them for the purposes of supply or to supply them.

This exemption can be cancelled or amended at any time by the APVMA.

APVMA CONTACT

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