Australian Government

Australian Pesticides and Veterinary Medicines Authority

Trade Advice Notice

on fluralaner in the product Exzolt Pour-on for Cattle for use on cattle

APVMA product number 92557

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This publication is available from the APVMA website.

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Preface

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking stakeholder involvement in decision making. Part of that process is the publication of Trade Advice Notices for all proposed extensions of use for existing products where there may be trade implications.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in regulatory guidance published on the APVMA website.

About this document

This Trade Advice Notice indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application to vary the use of an existing registered agricultural or veterinary chemical.

It provides a summary of the APVMA's residue and trade assessment.

Comment is sought from industry groups and stakeholders on the information contained within this document.

Making a submission

The APVMA invites any person to submit a relevant written submission as to whether the application to register Exzolt pour-on for Cattle should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These grounds relate to the trade implications of the extended use of the product. 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 by close of business on **19 July 2024** 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 to grant the application and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- contact name
- company or organisation name (if relevant)
- email or postal address (if available)

- the date you made the submission.

Please note: submissions will be published on the APVMA's website, unless you have asked for the submission to remain confidential, or if the APVMA chooses at its discretion not to publish any submissions received (refer to the public consultation coversheet).

Please lodge your submission using the public consultation 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.

Unless you request for your submission to remain confidential, the APVMA may release your submission to the applicant for comment.

Written submissions should be addressed to:

Residues and Trade
Risk Assessment Capability
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001

Phone: +61 2 6770 2300
Email: enquiries@apvma.gov.au

Further information

Further information can be obtained via the contact details provided above.

Further information on Trade Advice Notices can be found on the APVMA website: apvma.gov.au.

Introduction

The APVMA has before it an application from Intervet Australia Pty Ltd for approval of a new product, Exzolt pour-on for Cattle, containing 50 g/L fluralaner for the control of bush tick, buffalo fly and isoxazoline-susceptible strains of cattle tick.

The use of fluralaner on cattle has not previously been registered in Australia. Temporary MRLs were previously established under a research permit. Fluralaner is currently registered for oral administration to chickens via drinking water[1] and sheep vial oral drench[2].

As the proposed use is the first registration of fluralaner in cattle, the establishment of permanent MRLs and trade consideration is required.

[1] Australian Pesticides and Veterinary Medicines Authority (APVMA) - *Trade Advice Notice on fluralaner in the product EXZOLT Fluralaner Oral Solution for Chickens* - 7 November 2019 - APVMA website - accessed December 2023

[2] Australian Pesticides and Veterinary Medicines Authority (APVMA) - *Trade Advice Notice on fluralaner in the product Fluralaner 10 g/L Lousicide for Sheep for use in sheep* - 15 December 2022 - APVMA website - accessed December 2023

Trade considerations

Commodities exported

Cattle meat, offal and dairy products are considered to be major export commodities[3].

Destination and value of exports

In 2020–21, Australia exported a total of 940.2 kt of beef and veal worth $9.92B with significant export markets include China, Indonesia, Japan, the Republic of Korea and the United States[4]. Additional export markets for consideration are listed in the APVMA trade guidance for veterinary medicines[5].

Proposed Australian use pattern

The proposed use is for the dermal application of up to 3.7 mg fluralaner/kg bodyweight (1 mL of a 50 g/L product/20 kg bodyweight; nominal rate of 2.5 mg fluralaner / kg bodyweight) to cattle weighing 70 kg or more, in conjunction with a retreatment interval of 88 days. A meat withholding period of 38 days and an export slaughter interval of 88 days is proposed. A milk withholding period statement of 'DO NOT USE in female cattle which are producing or may in the future produce milk or milk products for human consumption except replacement dairy heifers prior to first mating' is proposed.

[3] Australian Pesticides and Veterinary Medicines Authority (APVMA) - *Overseas trade (Part 5B) Veterinary drug residues in food commodities and overseas trade* - 1 July 2014 - APVMA website - accessed December 2023.

[4] Australian Bureau of Agricultural and Resource Economics and Sciences (ABARES) - *Agricultural commodities and trade data* – 2022 – Rural commodities - meat - beef and veal - webpage – accessed December 2023

[5] Australian Pesticides and Veterinary Medicines Authority (APVMA) - *Veterinary data guidelines – Overseas trade (Part 5B)* - APVMA website - 1 July 2014 - accessed December 2023.

Table 1: Proposed label instructions for Exzolt pour-on for Cattle, containing 50 g/L fluralaner

<table>
<tr><td>Claims:</td><td>Exzolt Pour-on for Cattle is for the control of isoxazoline-susceptible strains of cattle tick (Rhipicephalus (Boophilus) microplus) including dieldrin, organophosphate, synthetic pyrethroid, amidine, macrocyclic lactone and fluazuron resistant ticks. Controls bush tick (Haemaphysalis longicornis), paralysis tick (Ixodes holocyclus) and buffalo fly (Haematobia irritans exigua) including synthetic pyrethroid resistant strains.
Cattle tick for 56 days
Bush tick for 21 days
Paralysis tick for 28 days
Buffalo fly for 35 days
Exzolt Pour-on for Cattle is a next generation ectoparasiticide. It contains fluralaner, a parasiticide belonging to the isoxazoline family of chemicals, which works systemically as well as by contact to control ectoparasites.

The efficacy of Exzolt Pour-on for Cattle is not adversely affected by heavy rainfall after treatment. Study data demonstrated that artificial rain applied by inverted sprinklers (equivalent to rainfall of 22–23 mm in a storm lasting approximately 20 minutes) 6, 12, or 24 hours following treatment did not adversely affect efficacy.

Resistance may develop to any chemical.</td></tr>
<tr><td>Restraints:</td><td>DO NOT USE in cows which are producing or may in the future produce milk that may be used or processed for human consumption except replacement dairy heifers prior to first mating.

DO NOT USE in animals weighing less than 70 kg.

Re-treatment interval: DO NOT re-treat animals for 88 days after last treatment.</td></tr>
<tr><td>Precautions:</td><td>Reproductive safety in breeding bulls has not been evaluated.</td></tr>
<tr><td>Side effects:</td><td>Topical treatment with Exzolt Pour-on for Cattle is generally well tolerated and no serious adverse reactions have occurred in the studies. Mild and transient local skin reactions may occur, which do not affect the general health of the animals and do not require specific treatment. If a skin reaction does occur, it is cosmetic in nature and will typically resolve within 41 days after treatment.</td></tr>
<tr><td>Dosage and administration:</td><td>Administer topically in a narrow strip along the midline of the back from the withers to the base of the tail. Cattle should be dry at treatment. Use in well-ventilated areas or outdoors.

Exzolt Pour-On for Cattle is safe for use in breeding and pregnant cows, however, reproductive safety in breeding bulls has not been evaluated.

Keep treated animals separated from untreated animals.

The recommended dose rate is 1 mL/20 kg body weight (equivalent to 2.5 mg Fluralaner per kg body weight).

Dose rate: 1 mL per 20 kg body weight.

The following table may be used as a guide:
<table>
<tr><th>Weight range (kg)</th><th>Dose volume (mL)</th></tr>
<tr><td>Less than 70</td><td>Do not treat</td></tr>
<tr><td>71 – 100</td><td>5.0</td></tr>
<tr><td>101 – 150</td><td>7.5</td></tr>
</table>
</td></tr>
</table>

151 – 200	10.0
201 – 250	12.5
251 – 300	15.0
301 – 350	17.5
351 – 400	20.0
401 – 450	22.5
451 – 500	25.0
501 – 550	27.5
551 – 600	30.0
601 – 650*	32.5

* Add 2.5 mL for each 50 kg above 650 kg.

A representative sample of animals should be weighed before treatment either with scales or a weighband.

Dose rate to be based on heaviest cattle in each group (bulls, cows, steers, calves, etc). Do not under dose.

Where there is a large variation in size within the group, draft into 2 or more lines based on bodyweight, to avoid excessive overdosing.

Apply only with the recommended applicator and draw off tube. Clean applicator with warm soapy water then flush with clean water and allow to dry before next use.

Withholding periods:

MEAT: DO NOT USE less than 38 days before slaughter for human consumption.

MILK: DO NOT USE in cows which are producing or may in the future produce milk that may be used or processed for human consumption except replacement dairy heifers prior to first mating.

Trade advice:

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 88 days before slaughter for export. Before using this product, confirm the current ESI from MSD Animal Health on 1800 226 511 or the APVMA website (www.apvma.gov.au/residues).

Results from residues trials presented to the APVMA

Metabolism and residues definition

In a study involving a topical dose of [^{14}C]-fluralaner to 28 beef cattle of various commercial breeds, levels of total radioactive residues (TRR) were determined in edible tissues at 7, 14, 21, 35, 42 or 60 days post dose.

The highest TRR concentrations were found in the liver and bile, followed by fat (renal, mesenterial), kidneys, fat at the application site (composite) and then muscle tissues (hind leg and application site). Over the course of the study, the TRR concentrations decreased in all tissue types sampled. Parent fluralaner was found to be the predominant component with minor concentrations of metabolite AH362502 (M5, a hydroxylated fluralaner metabolite) observed in all tissues, and hydroxy glutathione (GSH)-fluralaner (M11), GSH-fluralaner (M12), hydroxy-fluralaner (M4) and the isoxazole ring-opened fluralaner (M15) observed in the liver.

The ratio of marker residue to total residues (MR:TR) for fluralaner in cattle tissues ranged from 0.31–0.67 in liver, 0.71–0.84 in kidney, 0.74–0.93 in muscle (across all muscle tissues sampled), and 0.85–1.0 in fat (across all fat tissues sample) over the 60-day sampling period. It is concluded the appropriate residue definition for edible cattle tissues is parent fluralaner. The existing residue definition for fluralaner as parent fluralaner, which was established in support of the registered use in chickens and sheep, remains appropriate for cattle.

Analytical methods

Validated methods for the quantification of parent fluralaner residues in edible cattle tissue using LC-MS/MS methodologies were considered. The methods limit of quantification (LOQ) for liver and fat were 0.04 mg/kg, 0.02 mg/kg for kidney and 0.008 mg/kg for muscle. The limits of detection (LOD) were 0.014 mg/kg for liver, 0.013 mg/kg for fat, 0.008 mg/kg for kidney and 0.003 mg/kg for muscle.

Residues depletion studies

Three residue depletion studies were conducted to determine the residues of fluralaner in edible tissues of cattle following the topical application of the product Exzolt Pour-on or similarly formulated fluralaner pour-on solutions. Study animals were administered 3.7 to 4.0 mg/kg body weight applied topically along the backbone as a line starting from the withers heading to the tail head.

In the first study, tissue samples, including those from muscle (leg and at the site of application), fat (perirenal, mesenterial and subcutaneous at the site of application) as well as edible offals including liver, kidney, heart and tongue, were collected from groups of 6 animals (3 female, 3 male) per timepoint at 7, 14, 21, 35, 42, 61, 79, 112 days post-treatment and analysed for parent fluralaner residues. At day 35, which is the closest time-point to the proposed 38-day meat withholding period, all residues of fluralaner were below the proposed MRLs and ranged from <LOQ - 0.133 mg/kg in liver, <LOQ – 0.070 mg/kg in kidney, <LOQ – 0.020 mg/kg in muscle and <LOQ – 0.184 mg/kg in perirenal fat (which had a slightly higher residue than mesenterial fat). At day 61, mean residues in all tissues were less than their respective LOQ values. There were no detectable residues by day 112 (all below LOD).

In the second study, tissue samples, including those from muscle (application site), fat (perirenal), liver and kidney, were collected from groups of 6 animals (3 female, 3 male) per timepoint at 7, 21, 35, 42 and 84 days post-treatment and analysed for parent fluralaner residues. No quantifiable residues of fluralaner were reported by day 35 and beyond across all tissues sampled.

In the third study, tissue samples, including those from muscle (leg and at the site of application), fat (perirenal and omental) as well as edible offals including liver, kidney and tongue, were collected from groups of 6 animals (3 female, 3 male) per timepoint at 7, 21, 35, 42 and 84 days post-treatment and analysed for parent fluralaner residues. At day 35 all residues of fluralaner were below the proposed MRLs and ranged from <LOQ - 0.401 mg/kg in liver, <LOQ – 0.163 mg/kg in kidney, <LOQ – 0.048 mg/kg in muscle and <LOQ – 0.356 mg/kg in fat. At day 84, mean residues in all tissues were less than their respective LOQ values with the exception of tongue where the mean fluralaner residue was <0.01 mg/kg.

Based on the available data, MRLs at 0.6, 0.25, 0.25, 0.7 and 0.07 mg/kg for cattle liver, kidney, offal (other than kidney and liver), fat and muscle, respectively, are considered appropriate. Statistical analyses at the 95 percentile of the decline profile, confirms the proposed 38-day meat withholding period is appropriate for the proposed use in cattle.

The proposed label has the restraint ‘DO NOT USE in cows which are producing or may in the future produce milk that may be used or processed for human consumption except replacement dairy heifers prior to first mating.’ Given no residues data is available for estimation of fluralaner in cattle milk, this restraint is considered appropriate.

Overseas registration and approved label instructions

The applicant indicated that fluralaner products are registered for use on cattle in Argentina, Bolivia, Brazil, Mexico and Uruguay.

Codex Alimentarius Commission and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticides and veterinary medicines. Codex CXLs are primarily intended to facilitate international trade and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex CXLs when importing foods. Fluralaner has not been considered by Codex or other international regulators for use on cattle and no cattle or mammalian MRLs have been established by Codex or other international regulators.

Current and proposed Australian MRLs for fluralaner

Table 2: Proposed amendments to Table 1 of the APVMA maximum residue limit (MRL) standard

Compound	Food	MRL (mg/kg)
Fluralaner		
Delete:		
MF 0812	Cattle fat	T0.7
	Cattle muscle	T0.07
MO 1280	Cattle, kidney	T0.25
MO 1281	Cattle, liver	T0.6
Add:		
MF 0812	Cattle fat	0.7
	Cattle muscle	0.07
MO 0812	Cattle, edible offal of, {except; kidney, liver}	0.25
MO 1280	Cattle, kidney	0.25
MO 1281	Cattle, liver	0.6

Note: the current temporary MRLs for fluralaner in cattle tissues were established in support of a limited scale research permit.

Potential risk to trade

Export of treated produce containing finite (measurable) residues of fluralaner may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country.

Finite MRLs for cattle commodities are recommended at 0.6, 0.25, 0.25, 0.7 and 0.07 mg/kg for cattle liver, kidney, offal (other than kidney and liver), fat and muscle, respectively in support of the proposed pour-on treatment with a 38-day meat withholding period. Fluralaner residues at the proposed Australian MRLs may lead to a potential risk to trade in cattle tissues, as export markets do not have established MRLs.

As international markets have not established fluralaner MRLs for cattle tissues, the validated LOQ for cattle liver and fat are considered to be the appropriate export slaughter interval (ESI) endpoints at this time. Based on statistical analysis of the residue depletion data from the 3 GLP studies, residues of fluralaner are expected to be below the LOQ in fat and liver at the recommended ESI of 88 days.

Conclusion

The APVMA has before it an application from Intervet Australia Pty Ltd for approval of a new product, Exzolt pour-on for Cattle, containing 50 g/L fluralaner for the control of bush tick, buffalo fly and isoxazoline-susceptible strains of cattle tick.

Comments are sought on the potential risk to trade in edible cattle tissues from the proposed use and the ability of the industry to manage any potential risk.