Australian Government

Australian Pesticides and Veterinary Medicines Authority

Trade Advice Notice

on fluralaner in the product Fluralaner 10 g/L Lousicide for Sheep for use in sheep

APVMA product number 91565

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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 for approval of a new veterinary chemical product

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 Fluralaner 10 g/L Lousicide for Sheep 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 Thursday, 12 January 2023 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 Limited for approval of a new product, Fluralaner 10 g/L Lousicide for Sheep, containing 10 mg fluralaner/mL, for oral administration to sheep.

The use of fluralaner on sheep has not previously been registered in Australia. Fluralaner is currently registered for oral administration to chickens via drinking water[1].

Given that the currently proposed use is the first use of fluralaner in sheep (or any other mammal used for food production), consideration to the appropriate residue definition (marker residue) for fluralaner in sheep is required in addition to the establishment of MRLs for edible sheep tissues and consideration of potential trade implications.

[1] Australian Pesticides and Veterinary Medicines Authority, *Trade Advice Notice on fluralaner in the product EXZOLT Fluralaner Oral Solution for Chickens*, APVMA website, 7 November 2019, accessed 5 December 2022.

Trade considerations

Commodities exported

Edible sheep commodities (meat, fat, edible offal) are considered to be major export commodities[2].

Destination and value of exports

In 2020–21, Australia exported 280 kt of lamb (worth $2.5B) and 146 kt of mutton (worth $1.0B)[3].The significant export markets for sheep commodities are listed in APVMA trade guidance[4] and include China, the Middle East and the United States.

Proposed Australian use pattern

The proposed use is for the oral administration of up to 2.5 mg fluralaner/kg bodyweight (1.5 mL of a 10 g/L product/6 kg bodyweight; nominal rate of 1.5 mg fluralaner/kg bodyweight) to sheep weighing 6 kg or more, in conjunction with a retreatment interval of 54 days and meat withholding period of 14 days. A milk withholding period statement of 'DO NOT USE in ewes which are producing or may in the future produce milk that may be used or processed for human consumption' is proposed. An export slaughter interval of 54 days is also proposed.

Table 1: Proposed use pattern

Species	Claims	Dosage
Sheep and lambs	For the control of isoxazoline-susceptible lice (Bovicola ovis), including strains resistant to synthetic pyrethroids and insect growth regulators, on sheep and lambs.	Administration orally using drench equipment or syringes. The recommended dose rate is for up to 2.5 mg fluralaner/kg bodyweight (1.5 mL of a 10 g/L product/6 kg bodyweight; proposed nominal rate of 1.5 mg fluralaner/kg bodyweight).

Withholding periods:

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

[2]Australian Pesticides and Veterinary Medicines Authority, *Pesticides: Overseas trade (Part 5B)*, APVMA website, 20 July 2020, accessed 5 December 2022.

[3]Australian Bureau of Agricultural and Resource Economics and Sciences, *Agricultural commodities and trade data*, ABARES website, accessed 5 December 2022.

[4]Australian Pesticides and Veterinary Medicines Authority *Veterinary data guidelines – Overseas trade (Part 5B)*, APVMA website, 1 July 2014, accessed 5 December 2022.

MILK: DO NOT USE in ewes which are producing or may in the future produce milk that may be used or processed for human consumption.

WOOL HARVESTING INTERVAL: Nil.

Restraints:

DO NOT retreat animals for 54 days after last treatment.

DO NOT USE in sheep less than 6 kg body weight.

Trade advice: EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 54 days before slaughter for export. Before using this product, confirm the current ESI from Coopers Animal Health on 1800 226 511 or the APVMA website (apvma.gov.au/residues).

Results from residues trials presented to the APVMA

Metabolism and residues definition

In a study involving oral administration of [^{14}C]-fluralaner to 20 Rambouilett/Merino crossbred sheep, levels of total radioactive residues (TRR) were determined in edible tissues (3, 5, 7, 10 and 12 days following treatment).

The highest TRR concentration was found in the liver, followed by fat (subcutaneous, mesenterial and renal), kidney and muscle across time-points. Over the course of the study, the TRR concentrations decreased in all tissue types. The TRR (and parent fluralaner concentrations) in male sheep tissue samples were higher than the levels in female sheep tissue samples at Day 3 however, were comparable at subsequent time-points.

Parent fluralaner was found to be the predominant component in each tissue, except liver where a glutathione conjugate of fluralaner (M12) was the predominant component. Metabolite AH362502 (M5, a hydroxylated fluralaner metabolite), and a hydroxylated GSH-fluralaner conjugate (M11) and M12 were the primary metabolites in sheep tissues.

The ratio of (mean) parent fluralaner to total residue calculated at Day 12, the closest time-point to the proposed 14 day meat withholding period, was 0.10 in liver, 0.61 in kidney, 0.81 in muscle, 0.81 in renal fat, 0.85 in mesenterial fat[5], and 0.92 in subcutaneous fat.

It is concluded that the appropriate residue definition for edible sheep tissues is parent fluralaner. The existing residue definition for fluralaner as parent fluralaner, which was established in support of the registered use in chickens, remains appropriate.

[5] For mesenteric fat, due to low and <LOQ fluralaner concentration results yielding an artificially inflated ratio larger than 1 at Day 12, Day 10 results were considered.

Analytical methods

Validated methods for the quantification of parent fluralaner residues in edible sheep tissues using LC-MS/MS methodologies, were considered. The methods limit of quantification (LOQ) for liver, kidney and fat were 0.01 mg/kg, and 0.005 mg/kg for muscle (and heart tissue). The limit of detection (LOD) was 0.003 mg/kg for liver, kidney and fat, and 0.001 mg/kg for muscle (and heart tissue).

Residues depletion studies

In the critical GLP residue depletion study, sheep were administered 3.0 mg fluralaner/kg bodyweight orally (1.2× the maximum dose proposed) and tissue samples were collected from 6 animals (3 male, 3 female) on Days 1, 3, 5, 7, 10, 13, 21, 28, 35, 42 and 49. The results are summarised for all tissues and time-points below:

Table 2: A summary of the range and mean (indicated in brackets with bold, mg/kg) of fluralaner residues in sheep tissue samples following oral treatment with 3 mg fluralaner/kg bodyweight

Day	Liver	Kidney	Renal fat	Subcutaneous fat	Mesenterial fat	Loin muscle	Heart
1	2.744 – 8.059 (**4.70**)	0.798 – 2.322 (**1.43**)	1.857 – 4.903 (**3.35**)	0.949 – 3.492 (**2.17**)	1.399 – 4.37 (**2.99**)	0.227 – 1.026 (**0.51**)	0.544 – 1.424 (**0.95**)
3	0.721 – 1.288 (**1.07**)	0.22 – 0.427 (**0.35**)	0.662 – 1.225 (**1.0**)	0.601 – 1.362 (**0.99**)	0.67 – 1.638 (**1.26**)	0.0822 – 0.229 (**0.17**)	0.28 – 0.478 (**0.42**)
5	0.225 – 1.48 (**0.69**)	0.0779 – 0.473 (**0.22**)	0.205 – 1.741 (**0.68**)	0.365 – 1.486 (**0.68**)	0.276 – 1.953 (**0.81**)	0.025 – 0.339 (**0.14**)	0.0814 – 0.492 (**0.24**)
7	0.0464 – 0.878 (**0.37**)	0.0152 – 0.232 (**0.11**)	0.0477 – 0.739 (**0.33**)	0.053 – 0.758 (**0.35**)	0.0414 – 0.795 (**0.34**)	0.0067 – 0.188 (**0.071**)	0.0189 – 0.329 (**0.13**)
10	0.0218 – 0.577 (**0.22**)	<LOQ – 0.17 (**0.063**)	0.0184 – 0.579 (**0.20**)	0.0167 – 0.653 (**0.21**)	0.0187 – 0.578 (**0.19**)	<LOQ – 0.0639 (**0.026**)	0.0062 – 0.119 (**0.066**)
13	<LOQ – 0.228 (**0.07**)	<LOD – 0.0694 (**0.021**)	<LOQ – 0.168 (**0.051**)	<LOQ – 0.156 (**0.056**)	<LOQ – 0.159 (**0.052**)	<LOQ – 0.0416 (**0.012**)	<LOQ – 0.0729 (**0.021**)
21	<LOD – 0.151 (**0.031**)	<LOD – 0.0367 (**0.09**)	<LOD – 0.0828 (**0.018**)	<LOD – 0.107 (**0.023**)	<LOD – 0.0811 (**0.019**)	<LOD – 0.0204 (**0.005**)	<LOD – 0.0375 (**0.007**)
28	<LOD – 0.0265 (**<LOQ**)	<LOD – <LOQ (**LOQ**)	<LOD – 0.0166 (**<LOQ**)	<LOD – 0.0165 (**<LOQ**)	<LOD – 0.0142 (**<LOQ**)	<LOD – <LOQ (**<LOQ**)	<LOD – 0.00679 (**<LOQ**)
35	<LOD – 0.0171 (**<LOQ**)	<LOD – <LOQ (**<LOQ**)	<LOD – 0.0124 (**<LOQ**)	<LOD – 0.016 (**<LOQ**)	<LOD – 0.0077 (**<LOQ**)	<LOD – <LOQ (**<LOQ**)	<LOD – <LOQ (**<LOQ**)
42	<LOD – 0.0197 (**<LOQ**)	<LOD – <LOQ (**<LOQ**)	<LOD – 0.0192 (**<LOQ**)	<LOD – 0.0202 (**<LOQ**)	<LOD – 0.0182 (**<LOQ**)	N/A	<LOD – 0.0058 (**<LOQ**)
49	<LOD	<LOD	<LOD	<LOD	<LOD	N/A	<LOD

Liver, Kidney and Fat - LOD: 0.003 mg/kg, LOQ: 0.01 mg/kg; Muscle and Heart - LOD: 0.001 mg/kg, LOQ: 0.005 mg/kg

N/A = Not analysed

At Day 13, which is the closest time-point to the proposed 14 day meat withholding period, mean fluralaner residues were <LOQ-0.228 mg/kg in liver, <LOD-0.0694 mg/kg in kidney, <LOQ-0.0416 mg/kg in muscle and <LOQ-0.156 mg/kg in subcutaneous fat (which had a slightly higher residue potential than renal fat and mesenterial fat). At Day 49, residues in all tissues were less than the respective LOD values (0.003 mg/kg for liver, kidney and fat, and 0.001 mg/kg for muscle).

Based on the available data and statistical analyses at the 95 percentile of the decline profile, MRLs of 0.4, 0.15, 0.35 and 0.1 mg/kg for sheep liver, kidney, fat and muscle, respectively, are considered appropriate for the proposed use in sheep in conjunction with the proposed 14 day meat withholding period.

Overseas registration and approved label instructions

The applicant has indicated that fluralaner is not currently registered for use on sheep in any overseas markets.

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 sheep and no sheep or mammalian MRLs have been established by Codex or other international regulators.

Current and proposed Australian MRLs for fluralaner

Table 3: Proposed amendments to Table1 of the APVMA maximum residue limit (MRL) standard

Compound		Food	MRL (mg/kg)
Fluralaner			
Delete:			
MF	0822	Sheep fat	T*0.06
MM	0822	Sheep muscle	T*0.005
MO	1289	Sheep, kidney	T*0.025
MO	1289	Sheep, liver	T*0.05
Add:			
MF	0822	Sheep fat	0.35
MM	0822	Sheep muscle	0.1

Compound	Food	MRL (mg/kg)
MO 1288	Sheep, kidney	0.15
MO 1289	Sheep, liver	0.4

Note: the currently established temporary MRLs for fluralaner in sheep 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 sheep commodities are proposed at 0.4, 0.15, 0.35 and 0.1 mg/kg for sheep liver, kidney, fat and muscle, respectively in support of the proposed oral treatment with a 14 day meat withholding period. Fluralaner residues at the proposed Australian MRLs may lead to a potential risk to trade in sheep tissues, as export markets do not have established MRLs.

As international markets have not established fluralaner MRLs for sheep tissues, the validated LOQs of 0.01 mg/kg for sheep kidney, liver and fat and 0.005 mg/kg for muscle are considered to be the appropriate export slaughter interval (ESI) endpoint at this time. In the critical GLP residue depletion study, residues were <LOD (0.003 mg/kg for liver, kidney and fat; 0.001 mg/kg for muscle) at 49 days after treatment and statistical analysis of the residue depletion data confirms that the applicant's proposed ESI of 54 days should ensure that fluralaner residues in sheep muscle, fat, liver and kidney for export will be below quantifiable levels. The 54 day ESI should therefore help prevent a risk to international trade.

Conclusion

The APVMA has before it an application from Intervet Australia Pty Limited for approval of a new product, Fluralaner 10 g/L Lousicide for Sheep, containing 10 mg fluralaner/mL, for oral administration to sheep. Comments are sought on the potential risk to trade in edible sheep tissues from the proposed use and the ability of the industry to manage any potential risk.