Australian Government

Australian Pesticides and Veterinary Medicines Authority

Trade Advice Notice

on tulathromycin in the product Draxxin Injectable Solution for use on sheep

APVMA product number 60018

November 2021

ISSN 2200-3894 (electronic)

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
GPO Box 3262
Sydney NSW 2001 Australia

Telephone: +61 2 6770 2300

Email: communications@apvma.gov.au

This publication is available from the APVMA website.

Contents

List of tables

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 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 extend the use of Draxxin Injectable Solution to 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 **Wednesday 1 December 2021** 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:

Assistant Director, Communications

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 Zoetis Australia Pty Ltd to vary the registration of Draxxin Injectable Solution (containing 100 mg tulathromycin/mL) to extend the use of the currently registered injection product to sheep for the treatment of early stages of foot rot.

The injection use of tulathromycin is currently registered for cattle and pigs for the control of bovine and swine respiratory disease. The use of tulathromycin in sheep is not currently approved in Australia. The proposed use therefore requires the consideration of an appropriate residue definition (marker residue) for tulathromycin in sheep, maximum residue limits (MRLs) for sheep tissues, and the consideration of trade implications.

Trade considerations

Commodities exported

Edible sheep commodities (meat, fat and edible offal) are considered to be major export commodities[1].

Destination and value of exports

In 2019–20, Australia exported 280 kt of lamb (worth $2.7 billion) and 182 kt of mutton (worth $1.4 billion)[2]. The significant export markets for sheep commodities include China, the Middle East and the United States.

Proposed Australian use pattern

The proposed use of Draxxin Injectable Solution is for the intramuscular injection of 2.5 mg tulathromycin/kg bw to sheep.

Table 1: Proposed Australian use pattern of Draxxin Injectable Solution containing 100 mg/mL tulathromycin

Species	Claim	Dosage
Sheep	Draxxin Injectable Solution is indicated for the treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus.*	1 mL product/40 kg body weight (2.5 mg tulathromycin/kg body weight) by a single intramuscular injection in the neck.

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

[2] ABARES, *Agricultural commodities and trade data*, Department of Agriculture, Water and the Environment website.

Withholding periods:

Meat: DO NOT USE less than 28 days before slaughter for human consumption.

Milk: DO NOT USE in dairy sheep that are producing milk or may in the future produce milk for human consumption or processing.

Retreatment interval:

Sheep: DO NOT RE-TREAT sheep for 7 weeks after last treatment.

Trade advice:

Export slaughter interval (ESI): DO NOT USE less than 49 days before slaughter for export.

Before using this product, confirm the current ESI from Zoetis on 1800 814 883 or the APVMA website (apvma.gov.au/residues).

Results from residues trials presented to the APVMA

Metabolism and residue definition

The metabolism of tulathromycin in animals has previously been evaluated in cattle, swine, rats, and dogs. A radiolabelled residue depletion study in sheep was available for consideration of the proposed use.

Based on the radiolabelled study in sheep, the CP-60,300[3] compound (when expressed as parent equivalents) was considered an adequate marker residue for the proposed use of tulathromycin in sheep. No changes to the current residue definition for tulathromycin is required. The mean marker to the total radioactive residues ratios in liver, kidney, muscle, fat and injection site were 0.81, 0.85, 0.78, 0.95 and 0.88, respectively.

It is concluded that the currently established residue definition for tulathromycin as the sum of tulathromycin and its metabolites that are converted by acid hydrolysis to (2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-2-ethyl-3,4,10,13-tetrahydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylohexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one is appropriate for both the enforcement and dietary risk assessment related to the injection use on sheep.

Analytical methods

A validated HPLC/MS/MS method was provided for the determination of tulathromycin residues in ovine tissues. The Limit of Quantifications (LOQs) of the method were 50 µg/kg for muscle and fat, 200 µg/kg for

[3] (2R,3S,4R,5R,8R,1 0R,11R,12S,13S, 14R)-2-ethyl3,4,10,13- tetrahydroxy3,5,8,10,12,14- hexamethyl-11- [[3,4,6-trideoxy-3-(dimethylamino)-β- D-xylohexopyranosyl]oxy] -1-oxa-6- azacyclopentadecan -15-one

kidney and 300 µg/kg for liver. The LODs were 6 µg/kg, 10 µg/kg, 5 µg/kg and 11 µg/kg for muscle, fat, kidney and liver, respectively.

Residue depletion studies

A residues depletion study is available that addresses the proposed use of tulathromycin on sheep (a single intramuscular dose of tulathromycin within the range 2.5±0.04 mg/kg body weight in the neck region). Thirty-six sheep were included in the treatment group, and tissue samples were collected for analysis from 4 animals at 2, 4, 7, 14, 21, 28, 35, 42, and 49 days post treatment.

At the proposed meat withholding period of 28 days, all residues in kidney, muscle and fat were less than the respective LOQ values. In liver, residues were <LOQ (300 µg/kg), 302, 367 and 536 µg/kg at day 28.

Meat withholding period and MRLs

Statistical analysis at the 95% percentile of the decline curve, indicated that MRLs of 1 mg/kg for liver; 0.3 mg/kg for kidney, 0.15 mg/kg for muscle and 0.03 mg/kg for fat would be appropriate at the proposed 28 day meat withholding period. MRLs of 1 mg/kg for liver, 0.3 mg/kg for kidney and 0.15 mg/kg for muscle are considered appropriate based on this statistical analysis of the critical dataset. The establishment of a MRL at the LOQ value of 0.05 mg/kg for fat is considered appropriate as the statistically estimated MRL of 0.03 mg/kg is below the validated LOQ at 0.05 mg/kg and because residues were <LOQ at both 21 and 28 days after treatment.

Retreatment interval

The proposed retreatment interval of 7 weeks is considered appropriate to allow tulathromycin residues to decline to less than the respective LOQ values in muscle, fat, liver and kidney to prevent the accumulation of residues following consecutive treatments.

Milk withholding period

As no relevant milk residues data is available, the proposed sheep milk restraint ('DO NOT USE in dairy sheep that are producing milk or may in the future produce milk for human consumption or processing') is supported.

Overseas registration and approved label instructions

The applicant indicated that Draxxin Injectable Solution is registered in the United Kingdom. A European Medicines Agency (EMA) report[4] indicated that a 16 day withdrawal period is associated with injection in the neck of sheep at the same dose rate (2.5 mg/kg bw) as considered for the current application.

[4] European Medicines Agency, *EPAR summary for the public – Draxxin*, EMA website, September 2016.

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. Tulathromycin has not been considered by Codex. The following relevant international MRLs have been established for tulathromycin:

Table 2: International tulathromycin MRLs

Regulator	MRL (mg/kg)			
	Muscle	Fat	Liver	Kidney
Australia (proposed)	0.15	*0.05	0.1	0.3
Codex/JECFA	No tulathromycin MRLs currently established			
EU	0.45	0.25	5.4	1.8
Japan	MRLs established for cattle and pig commodities only			
USA	MRLs established for cattle and pig commodities only			
Taiwan	MRLs established for cattle and pig commodities only			
Korea	No tulathromycin MRLs currently established			

Current and proposed Australian MRLs for tulathromycin in sheep

Table 3: Current tulathromycin MRLs

Compound	Food	MRL (mg/kg)
Tulathromycin		
MF 0812	Cattle fat	0.1
	Cattle muscle	0.1
MO 1280	Cattle, kidney	1
MO 1281	Cattle, liver	3
	Pig fat/skin	0.3
	Pig muscle	0.5
MO 1284	Pig, kidney	3

Compound	Food	MRL (mg/kg)
MO 1285	Pig, liver	2

Table 4: Proposed tulathromycin MRLs for Table 1 of the MRL Standard

Compound	Food	MRL (mg/kg)
Tulathromycin		
ADD:		
MF 0822	Sheep fat	*0.05
MO 1288	Sheep, kidney	0.3
MO 1289	Sheep, liver	1
	Sheep muscle	0.15

Potential risk to trade

Export of treated produce containing finite (measurable) residues of tulathromycin 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 sheep commodities are likely to exceed a residue tolerance (import tolerance) established in the importing country. An Export Slaughter Interval (ESI) can help manage the potential risk to trade arising from the use of Draxxin Injectable Solution in edible sheep commodities. The ESI can be determined on the basis of tulathromycin residues in edible sheep commodities declining to below the standards applied by the major export markets for Australian edible sheep commodities.

The European Union (EU) has established sheep commodity MRLs for sheep fat, liver, kidney and muscle at higher levels than the proposed Australian sheep commodity MRLs. However, other major markets and Codex have not established tulathromycin MRLs for sheep commodities. The ESI end-point is therefore considered to be the method LOQ for the respective tissues to mitigate any undue prejudice to international trade in sheep commodities. The validated LOQs for sheep muscle, kidney, liver and fat are 0.05, 0.2, 0.3 and 0.05 mg/kg, respectively.

Residues in fat, kidney and muscle were less than the respective LOQ values 28 days after treatment. For liver, residues remained >LOQ at 28, 35 and 42 days after treatment. At the final time-point at day 49, residues in liver were <LOQ. Tulathromycin residues in sheep muscle, fat, liver and kidney are expected to decline to less than the respective LOQ values following 49 days of withdrawal. Based on these results, the APVMA supports a 49 day ESI.

Injection site residues

At the supported ESI of 49 days, residues were <LOQ (<0.005 mg/kg) in the tissue surrounding the injection site while finite residues (0.10 to 0.22 mg/kg) were observed in the injection site core.

While finite residues were observed at the injection site core in the submitted study 49 days after treatment, the product is to be administered in the neck where injection sites may be trimmed. It is also noted that injection site residues were not considered for the determination of the current ESIs for cattle and pigs on the Draxxin Injectable Solution label and the APVMA is not aware of trade issues related to tulathromycin in injection sites of cattle or pig meat. For these reasons, the APVMA is proposing that the expected residues in the injection site core following the proposed use of Draxxin Injectable Solution in sheep at the supported ESI of 49 days (driven by residues in liver) should not present an undue risk to international trade.

Conclusion

Comments are sought on the potential risk to trade in sheep muscle (including injection site tissues), fat, liver and kidney from the proposed use and the ability of the industry to manage any potential risk.