Australian Government

Australian Pesticides and Veterinary Medicines Authority

Macrolide Antibiotics (kitasamycin, oleandomycin and tylosin) Regulatory decisions

The reconsideration of products containing kitasamycin, oleandomycin and tylosin and approvals of their associated labels

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FOREWORD

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the Agricultural and Veterinary Chemicals Code Act 1994.

The APVMA has legislated powers to reconsider the approval of an active constituent, registration of a chemical product or approval of a label at any time after it has been registered. The reconsideration process is outlined in sections 29 to 34 of Part 2, Division 4 of the Agvet Codes.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product containing that chemical, or its label. The scope of each reconsideration can cover a range of areas including human health (toxicology, public health, work health and safety), the environment (environmental fate and ecotoxicology), residues and trade, chemistry, efficacy or target crop/animal safety. However, the scope of each reconsideration is determined on a case- by-case reflecting the specific issues raised by the new research or evidence.

The reconsideration process includes a call for data from a variety of sources, a scientific evaluation of that data and, following public consultation, a regulatory decision about the ongoing use of the chemical or product. The data required by the APVMA must be generated according to scientific principles. The APVMA conducts science and evidence-based risk analysis with respect to the matters of concern, analysing all the relevant information and data available.

In undertaking reconsiderations, the APVMA works in close cooperation with external experts including the Department of the Environment and Energy, the Department of Health, Food Standards Australia New Zealand (FSANZ), and the state departments of agriculture, as well as other expert advisers as appropriate.

This document sets out the regulatory decision (RD) relating to products containing kitasamycin, oleandomycin and tylosin. The review findings and regulatory decisions are based on information collected from a variety of sources and comments received from public consultation.

This RD on kitasamycin, oleandomycin and tylosin is available from the APVMA website at www.apvma.gov.au.

The assessment reports and review findings are summarised in the macrolide antibiotics Proposed Regulatory Decisions (PRD) report that was published in November 2017.

EXECUTIVE SUMMARY

Introduction

The APVMA began its reconsideration (hereafter referred to as review) of product registrations and label approvals of the macrolide antibiotics kitasamycin, oleandomycin and tylosin, in 2001.This review was initiated on the basis of concerns over potential risks to human health, specifically the transfer of antibiotic resistance to humans following use of these antibiotics in animals.

The decision to undertake this review was a direct result of two recommendations made in the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR)[1] report: '*The Use of Antibiotics in Food-Producing Animals: Antibiotic-Resistant Bacteria in Animals and Humans'* (September 1999). Of particular concern was the use of antibiotics as growth promotants in food-producing animals. In these circumstances macrolides are recommended for use at sub-therapeutic concentrations for extended periods of time. This dosing regimen appears to provide the highest selective pressure for resistance.

The review scope included consideration of public health targeting Antimicrobial Resistance (AMR) and efficacy aspects of product registrations and label approvals for the macrolide antibiotics kitasamycin, oleandomycin and tylosin. The focus was on those products approved for growth promotion purposes and/or other routine uses where the duration and dose level were the same, or very similar to, those used for growth promotion.

Review findings

In examining the issue of antibiotic resistance the APVMA commissioned a review of the scientific literature available in the public domain relating to antimicrobial resistance to the macrolides. The APVMA also reviewed a quantitative risk assessment of tylosin prepared by a registrant, and undertook an efficacy assessment of the growth promotant uses of these antibiotics. The findings of these assessments are summarised in the macrolide antibiotics Proposed Regulatory Decisions (PRD) report.

From the results of these assessments, it can be concluded that the risk of antibiotic resistance will always exist. However, every effort must be made to delay its emergence and reduce its impact on human health. While protecting human health is essential, effective antibiotics are also needed to treat animals, including both livestock and companion animals to ensure their continued health, welfare and productivity. Prudent use of antibiotics is one of the cornerstones in minimising the emergence of antimicrobial resistance. It is widely accepted by international and Australian scientific bodies that macrolide use for the sole purpose of growth promotion is not regarded as prudent use. Withdrawal of growth promotion claims from labels of macrolide antibiotics will form part of the solution to delay the development of antibiotic resistance.

Internationally, the growth promotion claims of macrolides were revoked in New Zealand in 2001. The use of antimicrobials as growth promotants in food-producing animals was officially withdrawn in the European Union (EU) by the European Commission in 2006. Both the United States (US) and Canada have either voluntarily phased out, or are in the process of phasing out, the use of medically important antimicrobials in food-producing

[1] JETACAR: Details on this committee and its work can be found in macrolide antibiotics PRD report.

animals for growth promotion and are also requiring the oversight of a veterinarian for the therapeutic uses of such drugs.

More recently, the Australian government has identified AMR as one of the biggest threats to human health. In 2015 a National Antimicrobial Resistance Strategy was announced, supported by $9.4 million to continue the fight against AMR through research and education up to 2019. The Government's strategy takes a 'One Health' approach to AMR by tackling it through partnerships between the inextricably linked areas of human, animal and environmental health.

Regulatory decisions

After consideration of all data and assessments, and all submissions to the proposed regulatory decisions report, the APVMA has made the following regulatory decisions to:

- **Vary** relevant particulars of registration and label approvals of selected products (as listed in Table 1) to:
  - **Delete** product claims and associated use instructions for growth promotion and improved feed conversion efficiency (in pigs)
  - **Add** the following restraint statement relating to prudent use of antimicrobials:

    'Prior to prescribing [Name of Product] investigate the use of non-antibiotic options. If [Name of Product] is indicated and selected for use, prudent prescribing practices (appropriate dose, duration and frequency to minimise treatment failure while minimising the emergence of antimicrobial resistance) must be adhered to.

    NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL.'
- **Affirm** these product registrations and label approvals once the necessary particulars and conditions have been varied
- **Cancel** all previous product label approvals that are not consistent with the review outcomes and
- **Cancel** the registrations and associated label approvals of the product **VET ONLY TRUBIN L-50 GROWTH PROMOTANT FOR PIGS (35806)**. The only use for this product is growth promotion which cannot be supported.

Appendix A (tables A1-A18) contains product specific label variations for all affirmed macrolide antibiotic products.

The review of macrolide antibiotics is concluded

These regulatory actions conclude the review of product registrations and label approvals of the macrolide antibiotics kitasamycin, oleandomycin and tylosin.

Phase-out periods

The APVMA has determined that the maximum legislative one-year phase-out period is appropriate for the continued supply and use of registered products bearing cancelled labels (Column 5 of Table 1), as well as the supply and use of product being cancelled. During this period, products may continue to be used according to the earlier approved label instructions.

1 INTRODUCTION

1.1 Macrolide antibiotics

Macrolide antibiotics are a group of veterinary antibiotics widely used to treat and prevent diseases and promote growth in food-producing animals. Macrolides demonstrate antimicrobial activity by inhibiting protein synthesis and thus, cell growth of susceptible bacteria. Macrolides are predominantly bacteriostatic and are active against both Gram-positive (*Streptococcus*, *Staphylococcus*, *Enterococcus* and *Arcanobacterium pyogenes*) and Gram-negative bacteria (*Actinobacillus pleuropneumoniae* and *Campylobacter*), as well as anaerobic bacteria such as *Brachyspira*, *Fusobacterium*, *Clostridium* etc and other organisms such as *Lawsonia*, *Mycoplasma*, *Chlamydia*, *Bordatella*, etc. However, there are marked differences between the relative activities of different macrolides against these organisms. *Escherichia coli, Salmonella* spp and other Enterobacteriaceae and non-fastidious Gram-negative non-fermentative bacteria (e.g. *Pseudomonas aeruginosa*) are intrinsically resistant to macrolides, as the structure of their outer membrane prevents the macrolide from reaching the ribosomal target in the cytoplasm. Macrolides are among the few substances available to treat serious *Campylobacter* infections.

1.2 APVMA review of macrolide antibiotics

The increasing prevalence of antibiotic-resistant bacteria is recognised as a public health concern as life-saving antibiotics are becoming less effective and there are few alternative treatment options available. It is widely accepted that antibiotic-resistant bacteria are selected every time an antibiotic is used. The overuse of antibiotics in human medicine is a major contributing factor for the increasing prevalence of resistant bacteria. Likewise, the overuse of antibiotics in food-producing animals contributes to the development of antibiotic resistance. Of particular concern is the use of antibiotics as growth promotants in food-producing animals. In these cases the antibiotics are administered at sub-therapeutic concentrations for extended periods, and it is this dosing regimen that appears to provide the highest selective pressure for resistance.

In 1998, the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) was established by the Australian Government to assess scientific evidence for the link between the use of antimicrobial growth promotants in livestock feeds and emergence of antibiotic resistance. The committee concluded that there was evidence for the transfer of AMR determinants from animals to humans. In its 1999 report, JETACAR made 22 recommendations for an AMR management program that focused on regulatory controls, monitoring and surveillance, infection prevention strategies, education and research.

Of the 22 recommendations made by JETACAR in the 1999 report, Recommendation 1 and 2 were relevant to the APVMA's role in regulation of macrolide antibiotics. The review of macrolide antibiotics only included those products containing either kitasamycin, oleandomycin or tylosin, where label claims indicated use for growth promotion purposes and/or other routine uses where the duration and dose level were the same, or very similar to, those used for growth promotion. The scope of the review included the following aspects of product registrations and label approvals for macrolide antibiotics:

- public health assessment (antimicrobial resistance); and
- efficacy

1.3 Submissions received during the consultation period

Following the APVMA publication of the PRD report in November 2017, eight submissions were received. Three submissions were received from registration holders DOX-AL AUSTRALIA PTY LTD (2) and ALLTECH LIENERT AUSTRALIA PTY LTD, one submission was received from the Commonwealth Chief Veterinary Officer, a joint submission was received from Australian Society of Infectious Diseases and Australian Society of Antimicrobials, one submission was received from Australian Pork Limited, one submission was received from the Royal Australian College of Physicians and one submission was received from Australian Lot Feeders' Association. All responses were strongly supportive of the APVMA proposed regulatory decisions. No further information or data submitted during this consultation. Therefore, these submissions do not necessitate a change to the review outcomes and proposed decisions as presented in the PRD report.

2 REVIEW DECISIONS

Based on the evaluation of the submitted data and information, the APVMA has made the following decisions with regard to the continued registration of products containing macrolide antibiotics tylosin, kitasamycin and oleandomycin registered for growth promotant and/or other routine uses where the duration and dose level were the same, or very similar to, those used for growth promotion in food-producing animals, and their associated label approvals in Australia.

2.1 Particulars of product registrations and label approvals varied, cancelled previous labels and affirmed product registrations and approvals

The APVMA determined that it was NOT SATISFIED that the products listed in Table 1 below meet the safety criteria as defined in sections 5A of the Agvet Code when they were used according to the instructions for use on the previously approved labels listed in Column 5 of Table 1.

However the APVMA has determined that the relevant particulars of product registrations and label approvals (namely, the instructions for use of the products) could be varied in such a way to:

- Remove all product claims and associated use instructions for growth promotion and improved feed conversion efficiency
- Add the following restraint statement relating to prudent use of antimicrobials, to the restraint section of the registration label particulars:

> 'Prior to prescribing [Name of Product] investigate the use of non-antibiotic options. If [Name of Product] is indicated and selected for use, prudent prescribing practices (appropriate dose, duration and frequency to minimise treatment failure while minimising the emergence of antimicrobial resistance) must be adhered to.
>
> NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL.'

Therefore the APVMA has VARIED the instructions for use of these products assigning a new label approval numbers as listed in Column 6 of Table 1 and to CANCELLED any previous label approvals so leaving only one approved label for each of these products as listed in Column 4 of Table 1.

These variations to label instructions now satisfy the requirements for continued product registration and the APVMA has AFFIRMED product registrations listed in Table 1 in accordance with Section 34A of the Agvet Code, as the labels have now been varied.

Label instructions

The amendments that have been made to the label instructions for each product are summarised in Appendix A.

Label approval numbers

The APVMA has given new approval numbers (Column 6 of Table 1) to uniquely identify the labels varied resulting from this review.

Table 1: Product registrations affirmed following variation of relevant particulars

Product number	Product name	Holder	Label approvals cancelled	Label approvals varied and no longer in force	New (varied) label approvals
Label variation: Removed all indications for stimulating growth and improving feed efficiency, added the restraint statement presented in Section 2.1					
45175	LIENERT TYLAN 50 PREMIX	ALLTECH LIENERT AUSTRALIA PTY LTD		45175/62500	45175/RV0318D
53703	TYLOMIX 100 TYLOSIN TARTRATE PREMIX	ABBEY LABORATORIES PTY LTD		53703/0502	53703/RV0318E
53752	TYLECO 250 GRANULAR	INTERNATIONAL ANIMAL HEALTH PRODUCTS PTY LTD	53752/1102 53752/0707 53752/0702 53752/0701 53752/0108 53752/0104	53752/55127	53572/RV0318F
54573	TYLECO 50 GRANULAR	INTERNATIONAL ANIMAL HEALTH PRODUCTS PTY LTD	54573/55132 54573/1201 54573/1102 54573/0807 54573/0702 54573/0108 54573/0104	54573/61777	54573/RV0318G
59908	TYLODOX 250	DOX-AL AUSTRALIA PTY LTD	59908/55525 59908/0609 59908/0206	59908/55915	59908/RV0318H
60283	CCD TYLOSIN 100 (TYLOSIN PHOSPHATE) PREMIX	CCD ANIMAL HEALTH PTY LTD	60283/0906	60283/1207	60283/RV0318I
60891	TYLODOX 50 G MICROGRANULATE FEED ADDITIVE	DOX-AL AUSTRALIA PTY LTD	60891/62024 60891/0207	60891/55916	60891/RV0318J
61913	PHARMASIN 250 GRANULAR PREMIX	HUVEPHARMA EOOD		61913/0809	61913/RV0318L

Product number	Product name	Holder	Label approvals cancelled	Label approvals varied and no longer in force	New (varied) label approvals
61977	PHARMASIN 100 GRANULAR PREMIX	HUVEPHARMA EOOD		61977/0710	61977/RV0318M
62888	TYLODOX 50	DOX-AL AUSTRALIA PTY LTD	62888/0308	62888/62023	62888/RV0318N
64657	TYLODOX 250 G MICROGRANULATE FEED ADDITIV	DOX-AL AUSTRALIA PTY LTD		64657/0110	64657/RV0318O
65360	TYLODOX 1000	DOX-AL AUSTRALIA PTY LTD	65360/50752	65360/101728	65360/RV0318P
67990	TYLOGRAN 250 BMP	DOX-AL ITALIA S.P.A.	67990/57231	67990/106331	67990/RV0318Q
81769	TYLODOX 100G	DOX-AL AUSTRALIA PTY LTD		81769/104023	81769/RV0318R
Label variation: Added the restraint statement presented in Section 2.1					
36790	ELANCO AF0091 TYLAN 100 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36790/1206 36790/0301 36790/01	36790/107498	36790/RV0318A
36791	ELANCO AF0050 TYLAN 50 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36791/61984	36791/107462	36791/RV0318B
36806	ELANCO AF0250 TYLAN 250 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36806/1106 36806/0402 36806/0301 36806/0104 36806/01	36806/107042	36806/RV0318C
61525	ELANCO AF0248 TYLAN GRANULAR TYLOSIN PHOSPHATE	ELANCO AUSTRALASIA PTY LTD	61525/0908 61525/0807	61525/110285	61525/RV0318K

2.2 Cancelation of registration and label approvals of growth promotion product containing kitasamycin

The APVMA has decided that it was NOT SATISFIED that the product listed in Table 2 below meet the safety criteria as defined in sections 5A of the Agvet Code. The only use for this product is growth promotion which cannot be supported.

The APVMA was also not satisfied that the relevant particulars or conditions of the registration of the product listed in Table 2 could be varied in such a way as to allow the approval or registration to be affirmed. Therefore the

APVMA has CANCELLED the registration and label approvals of the product listed in Table 2 in accordance with Section 34AA and Section 44(2) of the Agvet Code.

Table 2: Product registration and label approvals cancelled

Product number	Product name	Holder	Label approvals cancelled
35806	VET ONLY TRUBIN L-50 GROWTH PROMOTANT FOR PIGS	COUNTRY VET WHOLESALING PTY LTD	35806/113630 35806/53433 35806/48865 35806/0498 35806/01

2.3 Phase-out periods

The APVMA has determined under s 81(3)(b) of the Agvet Code that one-year phase-out period shall apply for the continued supply and use of registered products bearing cancelled labels (Column 5 of Table 1). During this time, products may continue to be used according to the earlier approved label instructions. After that period all product that is supplied should bear the varied approved label (Column 6 of Table 1).

The APVMA has determined under s 45A and s 45B of the Agvet Code that one-year phase-out period shall apply for possessing, having custody of or using VET ONLY TRUBIN L-50 GROWTH PROMOTANT FOR PIGS (35806) bearing cancelled labels. During this time, product may continue to be used according to the earlier approved label instructions.

Appendix

APPENDIX A: SUMMARY OF LABEL CHANGES

New restraint statement:

'Prior to prescribing [Name of Product] investigate the use of non-antibiotic options. If [Name of Product] is indicated and selected for use, prudent prescribing practices (appropriate dose, duration and frequency to minimise treatment failure while minimising the emergence of antimicrobial resistance) must be adhered to.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL.'

Changes to labels instructions: 50 g/kg Tylosin Oral Pre-mix products

Table A-1: Changes to the varied label for Product 36791 *Elanco AF0050 Tylan 50 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Restraints:**
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	**Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40–100 g/tonne feed	

Table A-2: Changes to the varied label for Product 45175 *Lienert Tylan 50 Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscesses	11 ppm	**Indications for Use:**
Pigs	Ileitis	40 g/tonne feed	**Delete** 'For use as an aid in stimulating growth, improving feed efficiency and for the prevention of ileitis in pigs' and **replace** with 'For the prevention of ileitis in pigs.'
	Stimulating growth	10–100 g/tonne feed	**Recommended levels for use:**
	Improving feed efficiency	10–100 g/tonne feed	**Delete** 'For use as an aid in stimulating growth, improving feed efficiency and for the prevention of ileitis in pigs' and **replace** with 'For the prevention of ileitis in pigs.'
			Delete all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
			Up to 20 kg liveweight, 20 to 50 kg liveweight and 50 kg to market.
			Restraints:
			Add the restraint statement presented in Section 2.1.

Table A-3: Changes to the varied label for Product 54573 *Tyleco 50 Granular*

Species	Indication	Dose rate	Changes
Cattle	Liver abscesses	11 ppm	**Indications for Use:** **Delete** 'For increased growth stimulation and improved feed efficiency in pigs.' **Dosage and administration:** **Delete** all uses and recommended dose rates for increased growth stimulation and improved feed efficiency in pigs: Up to 20 kg body weight, 20 to 50 kg body weight and over 50 kg to slaughter. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100g/tonne feed	
	Improving feed efficiency	10–100g/tonne feed	

Table A-4: Changes to the varied label for Product 60891 *Tylodox 50 G Microgranulate Feed Additive*

Species	Indication	Dose rate	Changes
Cattle	Liver abscesses	11 ppm	**Indications for Use:** **Delete** 'TYLODOX 50 G is used for increase growth stimulation and improved feed efficiency in pigs. **Dosage and administration:** **Delete** all uses and recommended dose rates for increased growth stimulation and improved feed efficiency in pigs: Up to 20 kg body weight, 20 to 50 kg body weight and over 50 kg to slaughter. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Table A-5: Changes to the varied label for Product 62888 *Tylodox 50*

Species	Indication	Dose rate	Changes
Cattle	Liver abscesses	11 ppm	**Indications for Use:** **Delete** 'TYLODOX 50 is used for increase growth stimulation and improved feed efficiency in pigs.' **Dosage and administration:** **Delete** all uses and recommended dose rates for increased growth stimulation and improved feed efficiency in pigs: Up to 20 kg body weight, 20 kg to 50 kg body weight and over 50 kg to slaughter. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Changes to labels instructions: 100 g/kg Tylosin Oral Pre-mix products

Table A-6: Changes to the varied label for Product 36790 *Elanco AF0091 Tylan 100 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 2.1.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Table A-7: Changes to the varied label for Product 53703 *Tylomix 100 Tylosin Tartrate Premix*

Species	Indication	Dose rate	Changes
Pigs	Enteric disease Stimulating growth Improving feed efficiency	40–100 g/tonne feed 10–100 g/tonne feed 10–100 g/tonne feed	**Indications for Use:** **Delete** 'For use as an aid in controlling enteric diseases susceptible to tylosin and as an aid in stimulating growth and improving feed efficiency in pigs' and **replace** with 'For use as an aid in controlling enteric diseases susceptible to tylosin.' **Dosage and administration:** **Delete** all uses and recommended dose rates for growth stimulation and improved feed efficiency in pigs: Up to 20 kg liveweight, 20–50 kg liveweight and 50 kg to market. **Restraints:** **Add** the restraint statement presented in Section 2.1.

Table A-8: Changes to the varied label for Product 60283 *CCD Tylosin 100 (Tylosin Phosphate) Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:** **Delete** 'As an aid in stimulating growth and feed conversion efficiency in pigs.' **Directions for Use:** **Delete** all uses and recommended dose rates for increased growth stimulation and improved feed efficiency in pigs: Up to 20 kg liveweight, 20 to 50 kg liveweight and 50kg to market weight. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis Enteric disease Stimulating growth Improving feed efficiency	40–100 g/tonne feed 40–100 g/tonne feed 10–100 g/tonne feed 10–100 g/tonne feed	

Table A-9: Changes to the varied label for Product 61977 *Pharmasin 100 Granular Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:** **Delete** 'For use as an aid in controlling enteric diseases susceptible to tylosin and as an aid in stimulating growth and improving feed efficiency in pigs' and **replace** with 'For use as an aid in controlling enteric diseases susceptible to tylosin.' **Recommended levels for use:** **Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs: Up to 20 kg liveweight, 20 to 50 kg liveweight and 50 kg to market. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Chickens	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Table A-10: Changes to the varied label for Product 81769 *Tylodox 100G*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:** **Delete** 'Tylodox 100G is used for prevention of ileitis in pigs and for increased growth stimulation and improved feed efficiency in pigs' and **replace** with 'Tylodox 100G is used for the prevention of ileitis in pigs.' **Directions for Use:** **Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs: Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Changes to labels instructions: 250 g/kg Tylosin Oral Pre-mix products

Table A-11: Changes to the varied label for Product 36806 *Elanco AF0250 Tylan 250 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Restraints:**
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	**Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Table A-12: Changes to the varied label for Product 53752 *Tyleco 250 Granular*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:**
Pigs	Ileitis	40–100 g/tonne feed	**Delete** 'For increased growth stimulation and improving feed efficiency in pigs'
	Enteric disease	40–100 g/tonne feed	**Directions for Use:**
	Stimulating growth	10–100 g/tonne feed	**Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
	Improving feed efficiency	10–100 g/tonne feed	Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter.
			Restraints:
			Add the restraint statement presented in Section 2.1.

Table A-13: Changes to the varied label for Product 59908 *Tylodox 250*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:**
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	**Delete** 'TYLODOX 250 is used for increased growth stimulation and improved feed efficiency in pigs.'
			Directions for Use:
Pigs	Ileitis	40–100 g/tonne feed	**Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
	Enteric disease	40–100 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter.
	Improving feed efficiency	10–100 g/tonne feed	**Restraints:**
			Add the restraint statement presented in Section 2.1.

Table A-14: Changes to the varied label for Product 61913 *Pharmasin 250 Granular Premix*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:**
			Delete 'For increased growth stimulation and improved feed efficiency in pigs.'
Pigs	Ileitis	40–100 g/tonne feed	**Directions for Use:**
	Enteric disease	40–100 g/tonne feed	**Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
	Stimulating growth	10–100 g/tonne feed	Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter.
	Improving feed efficiency	10–100 g/tonne feed	**Restraints:**
			Add the restraint statement presented in Section 2.1.

Table A-15: Changes to the varied label for Product 64657 *Tylodox 250 G Microgranulate Feed Additive*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:**
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	**Delete** 'TYLODOX 250 G Microgranulate feed additive is used for increased growth stimulation and improved feed efficiency in pigs.'
Pigs	Ileitis	40–100 g/tonne feed	**Directions for Use:**
	Enteric disease	40–100 g/tonne feed	**Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
	Stimulating growth	10–100 g/tonne feed	Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter.
	Improving feed efficiency	10–100 g/tonne feed	**Restraints:**
			Add the restraint statement presented in Section 2.1.

Table A-16: Changes to the varied label for Product 67990 *Tylogran 250 BMP*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:**
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	**Delete** 'TYLOGRAN 250 BMP is used for increased growth stimulation and improved feed efficiency in pigs.'
			Dosage and administration:
Pigs	Ileitis	40–100 g/tonne feed	**Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs:
	Enteric disease	40–100 g/tonne feed	Up to 20 kg body weight, 20 kg to 50 kg body weight and Over 50 kg to slaughter.
	Stimulating growth	10–100 g/tonne feed	**Restraints:**
	Improving feed efficiency	10–100 g/tonne feed	**Add** the restraint statement presented in Section 2.1.

Changes to label instructions: 260 g/kg Tylosin Oral Pre-mix product

Table A-17: Changes to the varied label for Product 61525 *Elanco AF0248 Tylan Granular Tylosin Phosphate*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 2.1.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Changes to label instructions: 903 g/kg Tylosin Oral Pre-mix product

Table A-18: Changes to the varied label for Product 65360 *Tylodox 1000*

Species	Indication	Dose rate	Changes
Cattle	Liver abscess	11 ppm	**Indications for Use:** **Delete** 'For increase growth stimulation and improved feed efficiency in pigs.' **Dosage and administration:** **Delete** all uses and recommended dose rates for stimulating growth and improving feed efficiency in pigs: Up to 20 kg body weight, 20 kg – 50 kg body weight and Over 50 kg to slaughter. **Restraints:** **Add** the restraint statement presented in Section 2.1.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

ABBREVIATIONS

Agvet Code	Agricultural and Veterinary Chemicals Code Act 1994
AMR	Antimicrobial resistance
APVMA	Australian Pesticides and Veterinary Medicines Authority
EC	European Commission
EU	European Union
FSANZ	Food Standards Australia New Zealand
g/kg	Grams per kilogram
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
mg	milligrams
ppm	Parts per million
PRD	Proposed Regulatory Decision
RD	Regulatory Decision
spp.	Species
US	United States