Australian Government

Australian Pesticides and Veterinary Medicines Authority

NOVEMBER 2017

Macrolide antibiotics (kitasamycin, oleandomycin and tylosin): proposed 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, occupational 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 proposed regulatory decision (PRD) relating to the active constituents kitasamycin, oleandomycin and tylosin and products containing kitasamycin, oleandomycin and tylosin when used in accordance with label instructions. The preliminary review findings and proposed regulatory decisions are based on information collected from a variety of sources.

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

SUBMISSIONS FROM THE PUBLIC ARE INVITED

This proposed regulatory decisions report:

- outlines the APVMA reconsideration process
- advises interested parties how to respond to the reconsideration
- summarises the technical assessments
- outlines the proposed regulatory action to be taken in relation to the continued approval and registration of macrolide antibiotics (kitasamycin, oleandomycin and tylosin) in Australia.

Preparing your comments for submission

When making your comments:

- clearly identify the issue and clearly state your point of view
- give reasons for your comments, supporting them, if possible, with relevant scientific information and indicating the source of the information you have used
- suggest to the APVMA any alternative risk management solutions you may have.

Please structure your comments in point form, referring each point to the relevant section in the report.

All submissions to the APVMA will be acknowledged in writing via email or by post.

When making a submission please include:

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

the date you made the submission.

Note that all submissions received are subject to the Freedom of Information Act 1982, the Privacy Act 1988 and the Agvet Code. All personal and confidential commercial information (CCI) material contained in submissions will be treated confidentially. (A full definition of 'confidential commercial information' is contained in the Agvet Code).

The closing date for submissions is 28 February 2018

Submissions can be sent to:

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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. The details of specific product registration and label approvals included in the review are presented in Table1 (Appendix A).

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 Section 3 of this report.

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 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.

[1] JETACAR: Details on this committee and its work found on Section 1.2.

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.

Proposed regulatory decisions

After consideration of all data and assessments, the APVMA proposes the following regulatory actions:

- **Vary** label approvals of selected products (as listed in Table 3) 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 once the necessary label variations have been made
- **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 **TRUBIN L-50 GROWTH PROMOTANT FOR PIGS (35806)**. The only use for this product is growth promotion which cannot be supported.

Appendix B (tables B1-B18) contains product specific label variations for all macrolide antibiotic products to be affirmed.

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 available substances available to treat serious *Campylobacter* infections.

1.2 Reasons for the 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. In addition, JETACAR recommended a prudent use code of practice for antibiotics be developed based on scientific understanding of the pressures that select for resistant bacteria, based on the following principles:

General
Antibiotics should be used only where the benefits are scientifically demonstrable and substantial
In general, the spectrum of the antibiotic used should be the narrowest to cover the known or likely pathogen
Single agents should be used unless it has been proved that combination therapy is required to ensure efficacy or reduce the selection of clinically significant resistance
The dosage should be high enough to ensure efficacy and minimise the risk of resistance selection and low enough to minimise risk of dose-related toxicity
Therapy
Choice of therapy should be based on either: (i) culture and sensitivity test results (directed therapy), or (ii) known common pathogens in the condition and their current resistance patterns (empirical therapy)
Duration should be as short as possible and should not exceed seven days unless there is proof that this duration is inadequate
Prophylaxis
Choice should be based on known or likely target pathogen(s)
Duration should be as short as possible. Single dose prophylaxis is recommended for surgical prophylaxis. Long-term prophylaxis in human and veterinary medicine should be administered only when it has been demonstrated that the benefits outweigh the risk of resistance selection or propagation

Antibiotic growth promotant use in food-producing animals does not satisfy the prudent use principles described above. In this case, the antibiotics are used at sub-therapeutic concentrations for their performance enhancing effects and at the expense of applying selective pressure for antibiotic-resistant bacteria.

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.

Recommendation 1 of the JETACAR report was that Australia adopt a conservative approach to minimise the use of antibiotics in humans and animals and, to further this policy, that in-feed antibiotics used in food-producing animals for growth promotant purposes, or other routine uses where duration and dose level are the same, or very similar, should not be used unless they:

- are of demonstrable efficacy in livestock production under Australian conditions
- are rarely or never used as systemic therapeutic agents in humans or animals, or are not considered critical therapy for human use, and
- are not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms.

Recommendation 2 of the JETACAR report was that the APVMA review the use of antibiotic growth promotants currently registered in Australia that do not fulfil the criteria listed in Recommendation 1 in terms of their impact on human and animal health, using a risk analysis approach and including a cost-benefit analysis. The macrolide antibiotics kitasamycin, oleandomycin and tylosin were included in this recommendation.

1.3 Scope of the review

The review of all products containing kitasamycin, oleandomycin and tylosin used 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, and their associated labels commenced in 2001. The scope of the review included the following aspects of product registrations and label approvals for macrolide antibiotics:

- public health assessment (antimicrobial resistance)
- efficacy

The basis for a review of the registration and approvals for a chemical is whether the APVMA is satisfied that the safety, efficacy and trade criteria listed in sections 5A, 5B and 5C of the Agvet Code for continued registration and approval are being met. These requirements are that the use of the product, in accordance with instructions approved, or to be approved, by the APVMA for the product or contained in an established standard:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues
- would not be likely to have an effect that is harmful to human beings
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment
- would be effective according to criteria determined by the APVMA by legislative instrument, and
- would not unduly prejudice trade or commerce between Australia and places outside Australia.

The APVMA also considered whether labels for containers for chemical products containing macrolide antibiotics meet the labelling criteria as defined in section 5D of the Agvet Code which requires that labels have adequate instructions relating to:

- the circumstances in which the product should be used
- how the product should be used
- the times when the product should be used
- the frequency of the use of the product
- the re-entry period after use of the product
- the withholding period after the use of the product
- disposal of the product and its container
- safe handling of the product and first aid in the event of an accident
- any matters prescribed by the regulations

1.4 Products included in the review of macrolide antibiotics

This review focuses on the assessment of three selected macrolides: kitasamycin, oleandomycin and tylosin. Kitasamycin, oleandomycin and tylosin are currently registered in Australia for the treatment and prevention of infections caused by susceptible bacteria, as well as in growth promotion and feed conversion in food-producing animals. 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.

There are 19 products containing either kitasamycin or tylosin that meet the criteria described in the paragraph above that are currently included in the review and are outlined in Table A-1 (Appendix A). Of the 19 registered products remaining in the review the following should be noted:

- there are no registered oleandomycin products remaining in this review
- the single kitasamycin-containing product is only registered for use as a growth promotant in pigs
- 18 tylosin products are approved for use in pigs for both growth promotion and/or other routine uses where the duration and dose level are the same, or very similar
- all 19 products are administrated orally, via feed

1.5 Regulatory options

There are three possible outcomes of the review of the macrolide antibiotics. Based on the information reviewed the APVMA may be:

- satisfied that the products and their labels continue to meet the prescribed requirements for registration and approval and therefore affirms the registrations and approvals
- satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration and approval will be complied with and therefore varies the conditions of registration or approval
- not satisfied that the requirements for continued registration and approval continue to be met and thus suspends or cancels the registration and/or approval.

1.6 Next steps for this review

In this PRD report certain regulatory actions are proposed based on the assessments conducted by the APVMA and its partner agencies.

Persons and organisations are invited to submit their comments and related information relevant to these proposed decisions directly to the APVMA. This consultation period continues for three months ending on Wednesday 28 February 2018.

At the end of the consultation period the APVMA will publish the submissions, assess the information received and will determine the final regulatory actions for this review.

2 INTERNATIONAL GUIDELINES AND/OR REGULATIONS ON PRUDENT USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

This information is collated from various sources for the information of stakeholders and community groups.

2.1 United States

In 2012, the US Food and Drug Administration (FDA) published the guidance document *The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*. Medically important antibiotic classes are those considered by the US FDA to be important for treatment of disease in humans and include aminoglycosides, lincosamides, macrolides, penicillins, streptogramins, sulphonamides and tetracyclines. In this document the FDA concluded that medically important antimicrobial products registered in the US for use in animal feed for production or growth promotion were not compliant with contemporary judicious use principles, as the purpose of administration was not to improve or maintain the health of the animal.

In December 2013, the FDA published another guidance document aimed at assisting the sponsors of affected registered products in voluntarily adhering with the above recommendations for phasing-out the use of medically important antimicrobials in food-producing animals for the purpose of growth promotion and phasing-in increased veterinary oversight of remaining therapeutic uses.

2.2 Canada

In a similar approach to that used in the USA, Health Canada's Veterinary Drugs Directorate (VDD) worked with affected drug sponsors in the removal of growth promotion claims of medically important antimicrobial drugs and strengthening the veterinary oversight of antimicrobial use in food animals. Health Canada published a notice to stakeholders that the VDD will continue to collaborate with and where possible, align with the US for an efficient transition for all involved parties over the same time period stipulated by the US FDA. In April 2014, the Canadian Animal Health Institute announced their intent to work with the VDD to align with the US' policy on prudent use of antibiotics.

The Public Health Agency of Canada (PHAC) acknowledged that indiscriminate or inappropriate use of antimicrobials is largely responsible for the spread of AMR. Thus, a number of initiatives aimed at strengthening the promotion of appropriate use in both human and veterinary medicine have been developed. Specifically, Health Canada will be involved in increasing veterinary oversight of the use of medically important antimicrobials in food-producing animals. In addition, the regulatory framework on veterinary medicines and medicated feeds will be strengthened to include facilitating access to alternative therapies.

2.3 Europe and the United Kingdom

In 1999, the European Commission (EC) proposed withdrawing authorisation of tylosin phosphate as a feed additive in animal feeds based on public health concerns, in that its ongoing use may contribute to the transfer of resistant bacteria or its resistant determinants from animals to humans. Tylosin is registered in Europe for oral administration (via feed or drinking water) to pigs, poultry (chickens and turkeys), cattle, sheep and/or goats, via veterinarian prescription only. In January 2006, authorisation for the use of antimicrobials for growth promotion was officially withdrawn by the EC.

2.4 New Zealand

The use of macrolide antibiotics in animals was reviewed by New Zealand's Ministry of Primary Industries in 2001. As an outcome of the review, all growth promotion claims of macrolides were revoked. The remaining prophylactic and therapeutic uses continued to be allowed under veterinary authorisation.

2.5 The World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE)

The WHO, OIE and FAO have a tripartite agreement that stress the need for a 'One Health' approach. The objective of this approach is to implement national action plans by the 2017 World Health Assembly (WHA) addressing the threat of AMR globally.

In December 2003 and March 2004, the FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance recommended that the OIE and WHO should develop lists of critically important antimicrobial agents in veterinary and human medicine, respectively. The November 2007 Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials identified a number of antimicrobials that were considered by both the WHO and OIE as critically important for human and animal health, respectively, including macrolides. Consequently, the Meeting report emphasised the importance of appropriate management measures aimed at mitigating the development of AMR and maintaining the efficacy of these antimicrobials. The Meeting identified three classes of antimicrobials that should be addressed as the highest priority for the development of these risk management strategies for the development of AMR: quinolones, 3rd and 4th generation cephalosporins and macrolides.

In 2011, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance published the 3rd revision of their list of Critically Important Antimicrobials for Human Medicine. Macrolides (including tylosin, oleandomycin and kitasamycin) were listed as critically important for human medicine. This recommendation was based on two criteria being met; that is, that there are limited alternative therapies for *Legionella*, *Campylobacter* and multi-drug-resistant *Salmonella* and *Shigella* infections and that AMR may result from transmission of *Campylobacter* spp. and *Salmonella* from non-human sources. In 2014, the OIE published a List of Antimicrobial Agents of Veterinary Importance, which listed macrolides (including tylosin, oleandomycin and kitasamycin) as critically important to veterinary medicine, due to their essential role against specific infections where there was a lack of sufficient therapeutic alternatives.

2.6 Codex Alimentarius Commission (Codex)

The Codex Alimentarius (food code) was established by the FAO and WHO to develop harmonised international food standards aimed at protecting consumer health and fair trade. In 2005, the Codex published the *Code of Practice to Minimise and Contain Antimicrobial Resistance* (the Code) in food-producing animals. Among other recommendations, the Code stipulates that responsible and prudent use of antimicrobials does not include the use of antimicrobials that belong to or are able to cause cross-resistance to classes of antimicrobial agents used for humans. In the absence of a risk analysis the registration of these antimicrobials should be terminated or phased out. The Code further stipulates that off-label use of antimicrobials for growth promotion should not be permitted. The Code reiterates that antimicrobials should only be used under a prescription from a licensed veterinarian and that they should not be used as an alternative for good management and farm hygiene, or other disease prevention methods (eg vaccination).

3 SUMMARY OF ASSESSMENTS AND PROPOSED FINDINGS

Following the announcement of the review in 2001, the APVMA received submissions of data and use pattern information from product registrants, state and territory chemical coordinators, industry representatives and the public. These submission were considered and assessed by the APVMA throughout the review.

In examining the issue of AMR the APVMA commissioned a review of the scientific literature available in the public domain relating to antimicrobial resistance to the macrolides. A quantitative risk assessment of tylosin prepared by a registrant was also reviewed and an efficacy assessment of the growth promotant uses of these antibiotics undertaken.

3.1 Public health assessment (antimicrobial resistance)

The public health antimicrobial risk assessment for the review of macrolide antibiotics was undertaken by the (then) Department of Agriculture, Fisheries and Forestry in 2003 and considered all the data and information submitted for the review, as well as literature available in the public domain. The purpose of this public health risk assessment was to determine the risk to human health with respect to AMR posed by the sub-therapeutic use of macrolide antibiotics in food-producing animals. This assessment concluded that there is qualitative evidence that antimicrobial use in animals can lead to resistance in bacteria or to their resistance genes being passed to humans via the food chain. However, there are no reports recording the specific transfer of macrolide resistance, from animals to humans, in *Campylobacter spp.* and *Enterococci spp.*, which are the two food-borne bacterial genera of concern in the context of macrolide antibiotics.

A quantitative assessment of human health impacts associated with the use of tylosin in animal feeds was submitted by a registrant. This assessment concluded that there is a very low risk that tylosin use in animal feed would adversely affect humans. In 2005 the APVMA had the report externally peer-reviewed. The reviewers were of the opinion that the risk assessment was not comprehensive enough to determine that the risk was very low.

The APVMA commissioned an assessment of the effects of sub-therapeutic administration of tylosin to food-producing animals on antimicrobial resistance in 2013. It concluded that tylosin is still a valuable antimicrobial for treatment and prevention of production-limiting diseases in pigs, poultry and cattle. However, Sub-therapeutic use of tylosin will encourage the emergence and maintenance of resistant strains not only to tylosin but also to the more important related veterinary macrolides such as tilmicosin and tulathromycin and the pleuromutilin tiamulin because of shared resistance determinants and to clindamycin and virginiamycin through the MLS_B (macrolide, lincosamide and streptogramin B) phenotype.

Co-location of tylosin resistance determinants also allows co-selection of resistance to unrelated antimicrobial classes such as tetracyclines, β-lactams, aminoglycosides and sulphonamides. Tylosin resistance determinants (and any co-located genes) are carried on a variety of mobile genetic elements and horizontal gene transfer allows wide dissemination of these genes to a range of related and unrelated bacterial genera. Importantly resistant zoonotic organisms carried by animals treated with tylosin at therapeutic or sub-therapeutic levels transfer to humans via the food chain (enteric organisms such as *Campylobacter* spp or enterococci) or direct contact with pigs, carcasses or pork (eg *Streptococcus suis*) and resistance determinants carried by these resistant strains can spread to other human pathogens. Apart from the direct effect of selecting for and maintaining resistant bacteria, the role of sub-therapeutic use of antimicrobials in increasing mutation rates and horizontal transfer of resistance genes must also be considered.

3.2 Efficacy assessment

APVMA commissioned an assessment of the efficacy studies submitted to the review. This assessment concluded that kitasamycin is efficacious in improving average daily weight gain in pigs between 4.7 kg and 35 kg. Tylosin has been shown to be effective in improving average weight gain in pigs under a range of conditions, although its effect on food conversion efficiency appears to be more variable. Tylosin, at labelled doses, has a significant effect on susceptible disease agents including *Brachyspira hyodysentriae*, *Lawsonia intracellularis*, *Mycoplasma hyopneumoniae*, *Erysipelothrix rhusiopathiae* and *Actinobacillus pleuropneumoniae,* which may explain the positive effect of tylosin on weight gain and food conversion efficiency. Tylosin has also been shown to control liver abscessation in feedlot cattle. No data supporting the claims of efficacy of oleandomycin were provided for this review.

3.3 Scheduling committee decision

At the commencement of the review, tylosin in premix formulations at concentrations of 50 ppm or less were classified in Schedule 5 (could be sold in retail outlets without a veterinary prescription) in the Standards for Uniform Scheduling of Medicines and Poisons (SUSMP), while all other formulations and concentrations were classified in Schedule 4 (where the products can only be supplied through veterinary prescription). As of 1 June 2014, all concentrations and uses of tylosin were reclassified into Schedule 4 in the SUSMP. Consequently, all current registered products containing kitasamycin, oleandomycin and tylosin are classified in Schedule 4. The previous Schedule 5 entry for tylosin was deleted and this action finalises Recommendation 6[2] of the JETACAR report; it specifically aligns the scheduling of tylosin with that of other antibiotics used in animal treatment by requiring veterinary prescription of the use of products containing tylosin.

[2] Recommendation 6 of JETACAR report: 'That all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only).'

3.4 Australia's approach to combating antimicrobial resistance

In response to increasing public concern about AMR in humans and the potential impact of agricultural use of antimicrobials, the Australian government established the JETACAR as outlined in Section 1.2. A Steering Committee was established to develop a Commonwealth government response to JETACAR's recommendations and the government published their response in 2000. In general, the government found that the JETACAR's recommendations aimed to meet the objective of responding to the threat of AMR by implementing strategies consistent with and complementary to global initiatives.

In May 2008 the Australian Veterinary Association (AVA) developed a Code of Practice for the prescription and use of antimicrobials as an appendix (Appendix 15) to the *AVA Guidelines for Prescribing, Authorising and Dispensing Veterinary Medicines*, to raise awareness about AMR and the importance of minimising its emergence. The Code of Practice highlights general principles of use, as well as responsibilities of the prescribing veterinarian, registrants and users of antimicrobials. The current Code of Practice outlines that the veterinarian must assess the clinical need for antimicrobials prior to prescription and must communicate the risk of AMR in humans and the need for prudent use in animals. The Code of Practice further outlines that following communication of these issues, users of antimicrobials must not use antimicrobials as a substitute for good feeding and animal husbandry practices and should use products according to the approved label directions or following written veterinary advice.

The AVA recommends that prescribing veterinarians choose antimicrobials based on an assessment of the susceptibility of the bacteria believed to be implicated, ideally following isolation and sensitivity testing, and that routine prophylactic dental care, parasite control, infection control, hygiene, animal husbandry and vaccination be practised in order to minimise the requirement for antimicrobials. Off-label use of antimicrobials should only be used on individual, isolated animals (not herds or groups of animals), should only be used where no appropriately labelled registered veterinary drug is available, and preferably only after sensitivity testing has been conducted. The AVA listed fighting AMR as one of its five strategic priorities for 2016. In collaboration with Animal Medicines Australia, the AVA began a three-year project in 2016 to develop best-practice antibiotic prescribing guidelines for livestock and horses.

In 2013, a Senate Inquiry was held to assess the progress in the implementation of the recommendations of the 1999 JETACAR meeting. Among the 10 recommendations from the Inquiry, the committee recommended that consideration be given to banning all antibiotics listed by the WHO as 'critically important in human medicine'. This list includes the macrolide class of antimicrobials, which is considered by WHO as critically important for humans because it meets both Criterion 1 (limited therapeutic options for *Legionella*, *Campylobacter* and multi-drug resistant *Salmonella* and *Shigella* infections) and Criterion 2 (it is used to treat diseases caused by bacteria, specifically *Campylobacter* spp. and *Salmonella*, which may be transmitted to humans from animals). The committee also recommended that an independent body be established to develop a strategy, report publicly on AMR data and measures taken to combat AMR, and to manage the response to AMR in Australia.

The Australian Antimicrobial Resistance Prevention and Containment (AMRPC) Steering Group was established in 2013. The AMRPC Steering Group is a collaboration between the Departments of Health, and Agriculture and Water Resources, with the Chief Medical Officer and Chief Veterinary Officer providing leadership to oversee the development and implementation of a national AMR strategy. As well as, providing clear governance and accountability arrangements for both new and existing initiatives.

The Australian Commission on Safety and Quality in Health Care published a report of the Australian One Health Antimicrobial Resistance Colloquium in 2013. The Colloquium was convened at the request of the AMRPC Steering Group, in order to allow collaboration between medical, veterinary and agricultural professionals, as well as policy makers, to inform the development and implementation of a National AMR Strategy for Australia. In this report, it was stressed that while Australia has a comparatively low rate of antimicrobial usage and resistance in livestock, complacency cannot be tolerated. Furthermore, it was noted that while there is little direct evidence for the spread of antimicrobial resistant bacteria from animals to humans in Australia, there is documented evidence overseas for such a relationship as well as the transfer of AMR genes from animal to human bacterial strains. Nevertheless, the report highlighted the significance of even low incidences of AMR infections in animals, as an individual case may involve a new resistance mechanism. One of the challenges identified for the animal sector was increased pressure to phase out the use of antimicrobials for growth promotion or prophylactic purposes, particular those within antibiotic classes commonly used in both humans and animals.

In 2012, the Australian Health Protection Principal Committee, and subsequently Australian Health Ministers Advisory Council endorsed the formation of The Antimicrobial Resistance Standing Committee (AMRSC). The Standing Committee is responsible for overseeing and providing expert advice on AMR in Australia. In 2014, the AMRSC published its antibacterial importance ratings, which were endorsed by the Australian Health Protection Principal Committee. Both animal and human antibiotics belonging to the macrolide class were rated ‘low’. A low importance rating implies that there are a reasonable number of alternative agents in different classes available to treat most infections even if antibiotic resistance develops. However, any resistance developed against these antibiotics in animals may lead to cross-resistance to other macrolides or even other groups of antibiotics which are used in humans (e.g., erythromycin and lincomycin). Furthermore, it should be noted that the other members of the MLS_B group, lincosamide and streptogramin B are rated ‘medium’ and ‘high’, respectively.

The National Antimicrobial Resistance Strategy

In 2015, the first National Antimicrobial Resistance Strategy to combat the threat of AMR in Australia was published. This strategy represents the first national, cross-sector response to the threat of antimicrobial resistance in Australia. It focuses predominantly on bacterial resistance and the rapid development of resistance to antibiotics. Development of the national strategy was led by the Australian Antimicrobial Resistance Prevention and Containment (AMRPC) Steering Group, chaired by the Secretaries of the Department of Health and Department of Agriculture and Water Resources.

The Strategy is aligned with the WHO’s Global Action Plan on AMR and outlines the following objectives for action between 2015 and 2019:

- communication, education and training programs to increase awareness and understanding of AMR
- implementation of antimicrobial stewardship programs for both human and animal health to ensure appropriate and judicious prescribing, dispensing and administering of antimicrobials
- coordinated surveillance and reporting system for AMR and antimicrobial usage in both humans and animals
- infection prevention and control guidelines for both humans and animals to prevent infections and the spread of AMR
- ongoing research via a national research agenda
- international partnerships and collaborations
- review of the current regulatory system

The Strategy proposed a comprehensive surveillance system, integrating human, animal and agriculture programs within a One Health framework, which could be used to support national AMR prevention and containment efforts. In response, the Department of Agriculture and Water Resources commissioned an analysis, with recommendations, of the surveillance and reporting of AMR and antibiotic usage in animals and agriculture in Australia. This detailed analysis recommended integrated surveillance options that met OIE standards and would generate data that were internationally comparable. In June 2016, the results of the first nationwide survey of antibiotic resistance in animals (pets and livestock) in Australia were announced. The survey identified low rates of resistance to critically important drugs in Australian animals; however, as of August 2016, resistance of *Campylobacter* spp. to tylosin had not been assessed. The major findings of the survey included:

- low rates of resistance to third-generation cephalosporins and fluoroquinolones in *E. coli* isolated from both companion animals (<10%) and livestock (<3% and <1%, respectively)
- absence of resistance to carbapenems in *E. coli* isolated from both companion animals and livestock

To ensure that the strategy is implemented effectively, a coordinated effort from various stakeholders from both the Australian and state and territory governments, regulators, various organisations and groups representing the human and animal health industries, academic researchers and consumers is required.

3.5 Conclusion

In summary, the risk of antibiotic resistance will always exist, however every effort must be made to delay its emergence and to minimise its impact on human health as well as animal health, welfare and productivity. While protecting human health is essential, effective antibiotics are also needed to treat animals, including both livestock and companion animals. All use of antimicrobials in humans, animals, plants and food processing technology has the potential to lead to resistance. Antibiotic resistance can pose a threat to public health where antibiotics important to human medicines become ineffective against bacterial human pathogens. However, some uses promote the emergence of antibiotic resistance more than others. Clearly antimicrobial resistance extends well beyond macrolide antibiotics and the scope of this review. However, the recommendations made in this report are centred around minimising the emergence of antimicrobial resistance where possible.

Antibiotic growth promotant use in food-producing animals does not satisfy the prudent prescribing practices. In particular, the sub-therapeutic concentrations used to encourage weight gain and enhance general health lead to the emergence of antibiotic-resistant bacteria. Withdrawal of growth promotion claims from labels of macrolide antibiotics will form part of the solution to delay the emergence of antibiotic resistance. Combining this with the addition of a restraint statement on labels promoting prudent use of these products will assist in reducing resistance for these antibiotics.

4 REVIEW OUTCOMES

4.1 Summary of the proposed regulatory decisions

The APVMA proposes the following regulatory actions:

- **Vary** label approvals of selected products (as listed in Table 3) 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 once the necessary label variations have been made
- **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 **TRUBIN L-50 GROWTH PROMOTANT FOR PIGS (35806)**. The only use for this product is growth promotion which cannot be supported.

Appendix B (tables B1-B18) contains product specific label variations for all macrolide antibiotic products to be affirmed.

4.2 Supported claims

Taking into consideration the finding of the assessments discussed above in Section 3, the following claims for use of products containing macrolide antibiotics are supported:

Table 1: Approved claims that are supported

Supported claims	
Tylosin	Reduction in the incidence of liver abscess in cattle
	As an aid in controlling enteric diseases susceptible to tylosin in pigs
	Treatment and prevention of ileitis in pigs
	As an aid in the control of necrotic enteritis caused by Clostridium perfringens in broiler and replacement chickens

4.3 Unsupported claims

Taking into consideration the finding of the assessments discussed above in Section 3, the following claims for use of products containing macrolide antibiotics are not supported. It is proposed that these be deleted from label instructions:

Table 2: Approved claims that are no longer supported

Unsupported claims	
Tylosin	Growth promotion and improved feed conversion efficiency in pigs
Kitasamycin	Growth promotion in pigs

4.4 Label restraints

The following restraint statement must be added 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'

4.5 Label approval numbers

The APVMA proposes to vary product labels to uniquely identify the labels resulting from this review. The new label approval numbers will be [product_number]/1117.

5 PROPOSED REGULATORY DECISIONS

Based on the evaluation of the submitted data and information, the APVMA proposes to make 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 association label approvals in Australia.

5.1 Vary particulars and/or conditions (of label approval), cancel previous labels and affirm product registrations

The APVMA proposes to decide under s34(1) of the Agvet Code, that it is NOT SATISFIED that the products listed in Table 3 below meet the safety criteria and/or the trade criteria and/or the efficacy criteria as defined in sections 5A, 5B, 5C and 5D of the Agvet Code.

However the APVMA also proposes to decide, under s34A of the Agvet Code, that the relevant particulars or conditions of the registration (or approval) can be varied in such a way to allow the registration or approval to be affirmed.

Therefore the APVMA is proposing to VARY the current label approval for these products assigning a new label approval numbers as listed in Table 3 and to CANCEL any previous label approvals so leaving only one approved label for each of these products.

These variations to label instructions would satisfy the requirements for continued product registration and the APVMA proposes that product registrations listed be affirmed once labels have been varied and previous labels cancelled.

Table 3: Product registrations to be affirmed following variation of approved labels

Product Number	Product name	Holder	Label approvals cancelled	Label approval varied and no longer in force	New label approval number
Proposed label variation: Remove all indications for stimulating growth and improving feed efficiency, add the restraint statement presented in Section 4.4					
45175	LIENERT TYLAN 50 PREMIX	LIENERT AUSTRALIA PTY LTD		45175/62500	45175/1117
53703	TYLOMIX 100 TYLOSIN TARTRATE PREMIX	ABBEY LABORATORIES PTY LTD		53703/0502	53703/1117

Product Number	Product name	Holder	Label approvals cancelled	Label approval varied and no longer in force	New label approval number
53752	TYLECO 250 GRANULAR	INTERNATIONAL ANIMAL HEALTH PRODUCTS PTY LTD	53752/1102 53752/0707 53752/0702 53752/0701 53752/0108 53752/0104	53752/55127	53572/1117
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	54573/1117
59908	TYLODOX 250	DOX-AL AUSTRALIA PTY LTD	59908/55525 59908/0609 59908/0206	59908/55915	59908/1117
60283	CCD TYLOSIN 100 (TYLOSIN PHOSPHATE) PREMIX	CCD ANIMAL HEALTH PTY LTD	60283/0906	60283/1207	60283/1117
60891	TYLODOX 50 G MICROGRANULATE FEED ADDITIVE	DOX-AL AUSTRALIA PTY LTD	60891/55916 60891/0207	60891/62024	60891/1117
61913	PHARMASIN 250 GRANULAR PREMIX	HUVEPHARMA EOOD		61913/0809	61913/1117
61977	PHARMASIN 100 GRANULAR PREMIX	HUVEPHARMA EOOD		61977/0710	61977/1117
62888	TYLODOX 50	DOX-AL AUSTRALIA PTY LTD	62888/0308	62888/62023	62888/1117
64657	TYLODOX 250 G MICROGRANULATE FEED ADDITIV	DOX-AL AUSTRALIA PTY LTD		64657/0110	64657/1117
65360	TYLODOX 1000	DOX-AL AUSTRALIA PTY LTD	65360/50752	65360/101728	65360/1117
67990	TYLOGRAN 250 BMP	DOX-AL ITALIA S.P.A.	67990/57231	67990/106331	67990/1117

Product Number	Product name	Holder	Label approvals cancelled	Label approval varied and no longer in force	New label approval number
81769	TYLODOX 100G	DOX-AL AUSTRALIA PTY LTD		81769/104023	81769/1117
Proposed label variation: Add the restraint statement presented in Section 4.4					
36790	ELANCO AF0091 TYLAN 100 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36790/1206 36790/0301 36790/01	36790/107498	36790/1117
36791	ELANCO AF0050 TYLAN 50 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36791/61984	36791/107462	36791/1117
36806	ELANCO AF0250 TYLAN 250 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	36806/1106 36806/0402 36806/0301 36806/0104 36806/01	36806/107042	36806/1117
61525	ELANCO AF0248 TYLAN GRANULAR TYLOSIN PHOSPHATE	ELANCO AUSTRALASIA PTY LTD	61525/0908 61525/0807	61525/110285	61525/1117

5.2 Cancel registrations of certain products with no supported uses

The APVMA proposes to decide under s34(1) of the Agvet Code, that it is NOT SATISFIED that the product listed in Table 4 below meet the safety criteria and/or the trade criteria and/or the efficacy criteria as defined in sections 5A, 5B, 5C and 5D of the Agvet Code.

The APVMA is also not satisfied that the relevant particulars or conditions of the registration of the product listed in Table 4 could be varied in such a way as to allow the approval or registration to be affirmed. Therefore the APVMA propose that the registration of the product listed in Table 4 be cancelled in accordance with Section 34AA of the Agvet Code.

Table 4: Product registrations to be cancelled

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

5.3 Phase-out periods

The APVMA proposes that the maximum legislative one-year phase-out period is appropriate for the continued supply and use of registered products bearing cancelled labels, as well as the supply and use of products being cancelled. During this time, products may continue to be used according to the existing label instructions

APPENDICES

APPENDIX A – LIST OF PRODUCT REGISTRATIONS AND LABEL APPROVALS

Table A-1: Product registrations and associated label approvals included in the review

Product Number	Product name	Holder	Product type	Active constituent	Label approval number
36790	ELANCO AF 0091 TYLAN 100 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	Oral powder, pre-mix	Tylosin	36790/107498 36790/1206 36790/0301 36790/01
36791	ELANCO AF0050 TYLAN 50 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	Oral powder, pre-mix	Tylosin	36791/107462 36791/61984
36806	ELANCO AF0250 TYLAN 250 TYLOSIN PHOSPHATE PREMIX	ELANCO AUSTRALASIA PTY LTD	Oral powder, pre-mix	Tylosin	36806/107042 36806/1106 36806/0402 36806/0301 36806/0104 36806/01
45175	LIENERT TYLAN 50 PREMIX	LIENERT AUSTRALIA PTY LTD	Oral powder, pre-mix	Tylosin	45175/62500
53703	TYLOMIX 100 TYLOSIN TARTRATE PREMIX	ABBEY LABORATORIES PTY LTD	Oral powder, pre-mix	Tylosin	53703/0502
53752	TYLECO 250 GRANULAR	INTERNATIONAL ANIMAL HEALTH PRODUCTS PTY LTD	Oral powder, pre-mix	Tylosin	53752/55127 53752/1102 53752/0707 53752/0702 53752/0701 53752/0108 53752/0104

Product Number	Product name	Holder	Product type	Active constituent	Label approval number
54573	TYLECO 50 GRANULAR	INTERNATIONAL ANIMAL HEALTH PRODUCTS PTY LTD	Oral powder, pre-mix	Tylosin	54573/61777 54573/55132 54573/1201 54573/1102 54573/0807 54573/0702 54573/0108 54573/0104
59908	TYLODOX 250	DOX-AL AUSTRALIA PTY LTD	Oral powder, pre-mix	Tylosin	59908/55915 59908/55525 59908/0609 59908/0206
60283	CCD TYLOSIN 100 (TYLOSIN PHOSPHATE) PREMIX	CCD ANIMAL HEALTH PTY LTD	Oral powder, pre-mix	Tylosin	60283/1207 60283/0906
60891	TYLODOX 50 G MICROGRANULATE FEED ADDITIVE	DOX-AL AUSTRALIA PTY LTD	Oral granule, pellet	Tylosin	60891/62024 60891/55916 60891/0207
61525	ELANCO AF0248 TYLAN GRANULAR TYLOSIN PHOSPHATE	ELANCO AUSTRALASIA PTY LTD	Oral powder, pre-mix	Tylosin	61525/110285 61525/0908 61525/0807
61913	PHARMASIN 250 GRANULAR PREMIX	HUVEPHARMA EOOD	Oral powder, pre-mix	Tylosin	61913/0809
61977	PHARMASIN 100 GRANULAR PREMIX	HUVEPHARMA EOOD	Oral powder, pre-mix	Tylosin	61977/0710
62888	TYLODOX 50	DOX-AL AUSTRALIA PTY LTD	Oral granule, pellet	Tylosin	62888/62023 62888/0308
64657	TYLODOX 250 G MICROGRANULATE FEED ADDITIVE	DOX-AL AUSTRALIA PTY LTD	Oral powder, pre-mix	Tylosin	64657/0110
65360	TYLODOX 1000	DOX-AL AUSTRALIA PTY LTD	Oral powder, pre-mix	Tylosin	65360/101728 65360/50752

Product Number	Product name	Holder	Product type	Active constituent	Label approval number
67990	TYLOGRAN 250 BMP	DOX-AL ITALIA S.P.A.	Oral powder, pre-mix	Tylosin	67990/106331 67990/57231
81769	TYLODOX 100G	DOX-AL AUSTRALIA PTY LTD	Oral powder, pre-mix	Tylosin	81769/104023
35806	TRUBIN L-50 GROWTH PROMOTANT FOR PIGS	COUNTRY VET WHOLESALING PTY LTD	Oral powder, pre-mix	Kitasamycin	35806/53433 35806/48865 35806/0498 35806/01

APPENDIX B – SUMMARY OF PROPOSED LABEL CHANGES

Proposed changes to directions for use 50 g/kg Tylosin Oral Pre-mix products

Use patterns to remain on varied label

Table B-1: Proposed indications for use for Product 36791 *Elanco AF0050 Tylan 50 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 4.4.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	

Table B-2: Proposed indications for use for Product 45175 *Lienert Tylan 50 Premix*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscesses	11 ppm	**Indications for Use:** **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.' **Recommended levels for use:** **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 4.4.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Table B-3: Proposed indications for use for Product 54573 *Tyleco 50 Granular*

Species	Indication	Dose rate	Changes proposed
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 4.4.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100g/tonne feed	
	Improving feed efficiency	10–100g/tonne feed	

Table B-4: Proposed indications for use for Product 60891 *Tylodox 50 G Microgranulate Feed Additive*

Species	Indication	Dose rate	Changes proposed
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 4.4.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Table B-5: Proposed indications for use for Product 62888 *Tylodox 50*

Species	Indication	Dose rate	Changes proposed
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 4.4.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Proposed changes to directions for use 100 g/kg Tylosin Oral Pre-mix products

Use patterns to remain on varied label

Table B-6: Proposed indications for use for Product 36790 *Elanco AF0091 Tylan 100 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 4.4.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Table B-7: Proposed indications for use for Product 53703 *Tylomix 100 Tylosin Tartrate Premix*

Species	Indication	Dose rate	Changes proposed
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 4.4.

Table B-8: Proposed indications for use for Product 60283 *CCD Tylosin 100 (Tylosin Phosphate) Premix*

Species	Indication	Dose rate	Changes proposed
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 4.4.
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 B-9: Proposed indications for use for Product 61977 *Pharmasin 100 Granular Premix*

Species	Indication	Dose rate	Changes proposed
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 4.4.
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 B-10: Proposed indications for use for Product 81769 *Tylodox 100G*

Species	Indication	Dose rate	Changes proposed
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 4.4.
Pigs	Ileitis	40 g/tonne feed	
	Stimulating growth	10–100 g/tonne feed	
	Improving feed efficiency	10–100 g/tonne feed	

Proposed changes to directions for use 250 g/kg Tylosin Oral Pre-mix products

Use patterns to remain on varied label

Table B-11: Proposed indications for use for Product 36806 *Elanco AF0250 Tylan 250 Tylosin Phosphate Premix*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 4.4.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Table B-12: Proposed indications for use for Product 53752 *Tyleco 250 Granular*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Indications for Use:** **Delete** 'For increased growth stimulation and improving feed efficiency 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 4.4.
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 B-13: Proposed indications for use for Product 59908 *Tylodox 250*

Species	Indication	Dose rate	Changes proposed
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.'
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 4.4.

Table B-14: Proposed indications for use for Product 61913 *Pharmasin 250 Granular Premix*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Indications for Use:**
Pigs	Ileitis	40–100 g/tonne feed	**Delete** 'For increased growth stimulation and improved 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 4.4.

Table B-15: Proposed indications for use for Product 64657 *Tylodox 250 G Microgranulate Feed Additive*

Species	Indication	Dose rate	Changes proposed
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 4.4.

Table B-16: Proposed indications for use for Product 67990 *Tylogran 250 BMP*

Species	Indication	Dose rate	Changes proposed
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 4.4.

Proposed changes to directions for use 260 g/kg Tylosin Oral Pre-mix products

Use patterns to remain on varied label

Table B-17: Proposed indications for use for Product 61525 *Elanco AF0248 Tylan Granular Tylosin Phosphate*

Species	Indication	Dose rate	Changes proposed
Cattle	Liver abscess	11 ppm	**Restraints:** **Add** the restraint statement presented in Section 4.4.
Poultry	Necrotic enteritis	100 mg/kg feed 7 days	
Pigs	Ileitis	40–100 g/tonne feed	
	Enteric disease	40–100 g/tonne feed	

Proposed changes to directions for use 903 g/kg Tylosin Oral Pre-mix products

Use patterns to remain on varied label

Table B-18: Proposed indications for use for Product 65360 *Tylodox 1000*

Species	Indication	Dose rate	Changes proposed
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 4.4.
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
AMRPC	The Australian antimicrobial resistance prevention and containment steering group
AMRSC	Antimicrobial Resistance Standing Committee
APVMA	Australian Pesticides and Veterinary Medicines Authority
AVA	Australian Veterinary Association
E. coli	Escherichia coli
EC	European Commission
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FSANZ	Food Standards Australia New Zealand
g/kg	Grams per kilogram
JETACAR	Joint Expert Technical Advisory Committee on Antibiotic Resistance
mg	milligrams
MLS	Macrolides, lincosamides and streptogramins
MLS_B	Macrolide, lincosamide and streprogramin B
OIE	World Organisation for Animal Health
PHAC	Public Health Agency of Canada
ppm	Parts per million
PRD	Proposed Regulatory Decision
spp.	Species
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (formerly the Standard for the Uniform Scheduling of Drugs and Poisons)
US	United States
US FDA	United States Food and Drug Administration
VDD	Veterinary Drug Directorate
WHA	World Health Assembly
WHO	World Health Organisation