Australian Government

Australian Pesticides and Veterinary Medicines Authority

Neomycin

Review Technical Report

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Preface

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 Agricultural and Veterinary Chemicals Code (the Code), which is 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. The Code provides for the suspension and cancellation of approvals and registrations if it appears to the APVMA that the criteria for approval or registration are not, or are no longer, satisfied (s 41 and s 44 of Part 2, Division 5).

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 or animal safety. However, the scope of each reconsideration is determined on a case-by-case basis 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 scientific and evidence-based risk analysis with respect to the matters of concern by analysing all the relevant information and data available.

About this document

This Technical Report is intended to provide an overview of the assessments that have been conducted by the APVMA and of the specialist advice received from external experts and advisory agencies. It has been deliberately presented in a manner that is likely to be informative to the widest possible audience, thereby encouraging public comment.

This document contains a summary of the assessment reports generated in the course of the chemical review of an active ingredient, including the registered product and approved labels. The document provides a summary of the APVMA's assessment, which may include details of the:

- chemistry of the active constituent
- toxicology of both the active constituent and product
- residues and trade assessment
- occupational exposure aspects
- environmental fate, toxicity, potential exposure and hazard
- efficacy and target crop or animal safety.

Further information

Further information can be obtained via the contact details provided below. More details on the chemical review process can be found on the APVMA website: www.apvma.gov.au

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Introduction

Neomycin is an aminoglycoside antibiotic that displays bactericidal activity. It is contained in a variety of veterinary preparations for use in companion and food-producing animals. These products are used primarily to treat, prevent and/or control bacterial infections caused by various gram-negative bacteria sensitive to neomycin. The registration of neomycin was nominated for reconsideration due to concerns relating to residues violations in food-producing animals treated with oral, intramammary and injectable preparations of neomycin, and concerns relating to target animal safety. No residue or animal safety concerns were identified for topical formulations containing neomycin, or for small animal vaccines and semen extender powder preparations that contain neomycin as a preservative.

Purpose of review

The scope of the neomycin review is limited to the registrations and labels of products containing neomycin which are oral, intramammary and injectable preparations and includes the following aspects of product registrations and label approvals:

- Residues and Trade:
  - Residues in treated animals arising from application in accordance with label instructions
  - Establishment of appropriate maximum residue limits (MRLs) for supported uses
  - Risks to international trade resulting from the use of neomycin in animal species producing major export commodities
- Target animal safety
  - The potential for use of the products to result in deleterious effects on target animals
  - Whether labels include adequate instructions and warning statements

The APVMA has also considered information pertaining to the chemistry (of the active and products), toxicology (health-based guidance values and poison scheduling), worker health and safety (exposure during handling and application and establishment of appropriate first aid instructions and safety directions) and whether mitigation is required to reduce risk to the environment through use of the products.

In addition to the above assessments, neomycin labels were reviewed for consistency with current APVMA policies and guidelines, including the Veterinary Labelling Code.

Product claims and use patterns

There are currently 31 products registered for use in Australia that contain neomycin. However, only 9 registered products fall within the scope of the reconsideration, including oral, intramammary or injectable antibiotic formulations containing neomycin. The remaining 22 products are not within the scope of this review.

Oral antibiotic formulations that contain neomycin include feed additive powders, water soluble powders, solid dose tablets and oral suspensions. They are used primarily to treat bacterial enteritis in food producing and companion animals, and are approved for use in cattle, calves, poultry, horses, cats and dogs. Intramammary antibiotic formulations containing neomycin are used for the treatment of mastitis in lactating cattle. Injectable neomycin products are approved for the control of neomycin sensitive organisms in horses, cattle, pigs, dogs and cats.

Mode of action

Aminoglycoside antibiotics, such as neomycin, are predominately active against aerobic gram-negative bacteria in a concentration-dependant manner, with significant post-antibiotic effect. Neomycin inhibits bacterial protein synthesis through irreversible binding to the 30 S ribosomal subunit of susceptible bacteria. Aminoglycosides have little or no action against anaerobic bacteria, as they require oxygen to cross the cell membrane (Mercer 2022, Reeves 2011). Neomycin is known to be active against strains of gram-negative bacteria (excluding *Pseudomonas* spp.), such as E.coli, *Salmonella* and *Klebsiella* spp. and many strains of Staphylococcus aureus although treatment of staphylococci should be in conjunction with synergistic antibiotics, such as β-lactams (EMA 2002, Plumb 2002, Renshaw *et al*. 2003).

Aminoglycosides exert their antibacterial activity by interfering with protein synthesis at the membrane-associated bacterial ribosome (Riviere & Spoo 2001). This is achieved by irreversibly binding to one or more receptor proteins on the 30S subunit of the bacterial ribosome and subsequently interfering with the mRNA translation process, ultimately resulting in the production of a non-functional protein (EMA 2002, Reeves 2011). For neomycin to reach the ribosomal binding site of gram-negative bacteria, it must cross the bacterial cell wall and then the cell membrane. Initially, neomycin diffuses across the cell wall by competitive displacement of bridging divalent cations (such as Mg^{2+} or Ca^{2+}) and subsequent disruption of cross-links between adjacent lipopolysaccharides. This damages the cell wall and increases permeability, which allows the aminoglycoside to enter the periplasmic space in a passive and non-energy-dependent process. From there, it is actively transported across the cytoplasmic membrane via an oxygen- and energy-dependent interaction that is dependent on electron transport.

The bacterial cytoplasm is negatively charged with respect to the periplasm and external environment; thus, neomycin is transported across the cytoplasmic membrane by the membrane potential, where it is then able to interact with the ribosome and cause misreading of the mRNA. This further affects cell permeability, which allows more neomycin into the cell and leads to more cell disruption and eventually, cell death (Reeves 2011). The efficacy of aminoglycosides is substantially reduced in an anaerobic environment because the appropriate oxygen-dependent transport mechanisms described above are lacking (EMA 2002, Riviere & Spoo 2001).

Concentration-dependent killing

Aminoglycosides are bactericidal at higher concentrations, meaning they act by killing bacterial microorganisms rather than slowing or inhibiting their reproduction. They also exhibit concentration-dependent bacterial killing, where the peak concentration (C_{MAX}) is more important in determining the efficacy of bacterial killing than time above the minimum inhibitory concentration (MIC) (Freeman *et al*. 1997). Thus, it is more important to achieve optimal peak concentrations than to maintain drug concentrations slightly above the MIC for extended periods of time. While optimum ratios between the peak concentration and MIC have not yet been determined, the literature suggests that peak concentration, MIC ratios of 8:1 to 10:1 are necessary for optimal bactericidal activity while avoiding bacterial regrowth (Freeman *et al*. 1997, Huth *et al*. 2011).

Post-antibiotic effect

Aminoglycosides also exhibit a post-antibiotic effect (PAE), where bactericidal action persists after serum concentrations of neomycin drop below the MIC (Reeves 2011, Riviere & Spoo 2001). The exact mechanism of PAE has not yet been determined. The PAE of aminoglycosides is dependent on the:

- bacterial strain and its MIC
- duration of exposure of bacteria to the aminoglycoside
- inherent potency of the aminoglycoside
- concentration of the aminoglycosides (the higher the concentration, the longer the duration of the PAE).

Longer intervals between dosing (e.g. once-daily dosing) that provide a drug-free period in which bacteria are not exposed to the drug appear to preserve bactericidal activity of aminoglycosides and reduce the risk of antimicrobial resistance (AMR), as well as toxicity (Freeman *et al*. 1997). Studies in animal models have shown that the degree of cochlear damage induced by aminoglycosides is more dependent on the total daily dose than the frequency with which it is administered. It has been hypothesized that extended-interval dosing may result in less saturation of cochlear cells and accumulation of aminoglycosides than more frequent administration (Freeman *et al*. 1997).

Pharmacokinetics and metabolism

Absorption

Neomycin is a positively charged molecule with a high degree of polarity. This translates to very poor gastrointestinal absorption, typically less than 10%. However, substantial disruption of the intestinal mucosa, as may occur during cases of enteritis may increase gastrointestinal permeability and drug absorption. This is of particular concern in animals with impaired renal function where excretion of the absorbed drug is also compromised, potentially resulting in neomycin accumulation and subsequent nephrotoxicity (Mercer 2022).

Intramuscular administration of neomycin results in fast and near complete systemic absorption. Intramammary administration of aminoglycosides such as neomycin results in effective local concentration without significant systemic absorption. However, there is some concern relating to local tissue residues and residues in milk following intramammary administration which will be addressed in this review.

Distribution, metabolism and excretion

Neomycin binds weakly to plasma proteins, is poorly lipid-soluble and is highly polar at physiological pH. These characteristics generally reduce its systemic distribution and ability to cross cell membranes. However, accumulation of aminoglycosides and its metabolites is known to occur in the endolymph of the inner ear and the renal tubules.

Orally administered aminoglycosides are eliminated unchanged in the faeces in healthy animals. Following parenteral administration, neomycin is excreted unchanged primarily by renal glomerular filtration, with 80 to 90% of administered neomycin excreted in the urine (within 24 hours following intramuscular administration) (Reeves 2011, Riviere & Spoo 2001, Huth *et al*. 2011).

Glomerular filtration rates vary between species and are usually less in neonates, which are generally more sensitive to aminoglycosides (Mercer 2022). Furthermore, excretion varies as a result of changes to glomerular filtration rates in association with both cardiovascular and renal function, age, etc., and the half-life varies in response to the volume of extracellular fluid.

Aminoglycosides have relatively short plasma half-lives of approximately one hour in carnivores and 2 to 3 hours in herbivores and the elimination kinetics generally follow a 3-compartment model.

- First ‘deep’ phase: binding of drug in renal tubular cell
- β-phase: approximately 90% of the drug is excreted unchanged from the kidneys
- Second ‘deep’ (or γ phase): remaining drug excreted over protracted period (gradual release from renal intracellular binding sites; terminal elimination half-life 20 to 200 hours)

Chemistry

Neomycin is a mixture of compounds, principally the largest component, neomycin B, neomycin C which is an isomer of neomycin B and comprises 3 to 15% of the mixture, and minor compounds, such as neomycin A, which present at lower levels (less than 2%). Neomycin is most commonly available as the sulfate salt.

There are monographs for neomycin sulfate in the British Pharmacopeia (BP) and the US Pharmacopeia (USP). The BP monograph stipulates a minimum content (potency) of 680 IU/mg (dried substance), while the USP stipulates a potency equivalent to not less than 600 µg of neomycin per mg, calculated on the dried basis. The active contents for both monographs are determined using microbial assay methods.

The BP monograph for neomycin sulfate also specifies appearance, solubility, identification, pH, specific optical rotation, related substances (impurities), sulfate (27.0 to 31.0%), loss on drying (maximum 8.0%) and sulfated ash (maximum 1.0%). The USP monograph of neomycin sulfate also includes tests for identification, impurities, contents of neomycin A and C relative to B, pH and loss on drying with the same limits as those in the BP monograph. Limits for sterility and bacterial endotoxins can additionally be specified if required.

Active constituent

Tables 1 and 2 below show the nomenclature, structural formula and key physicochemical properties of the active constituent neomycin.

Table 1: Nomenclature and structural formula of the active constituent neomycin

Parameter	Nomenclature and structure
Common name (AAN, BP, BAN)	Neomycin (sulfate)
IUPAC name	(2*R*,3*S*,4*R*,5*R*,6*R*)-5-amino-2-(aminomethyl)-6-[(1*R*,2*R*,3*S*,4*R*,6*S*)-4,6-diamino-2-[(2*S*,3*R*,4*S*,5*R*)-4-[(2*R*,3*R*,4*R*,5*S*,6*S*)-3-amino-6-(aminomethyl)-4,5-dihydroxyoxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxycyclohexyl]oxyoxane-3,4-diol;sulfuric acid
CAS registry numbers	1404-04-2 (neomycin), 1405-10-3 (neomycin sulfate – unspecified sulfate content), 119-04-0 (neomycin B), 25389-98-4 (neomycin B sulfate (1:1)), 4146-30-9 (neomycin B sulfate (1:3))
Molecular formula (unspecified sulfate content)	$C_{23}H_{46}N_6O_{13}$,xH_2SO_4
Molecular weight	614.644 g/mol (neomycin base)

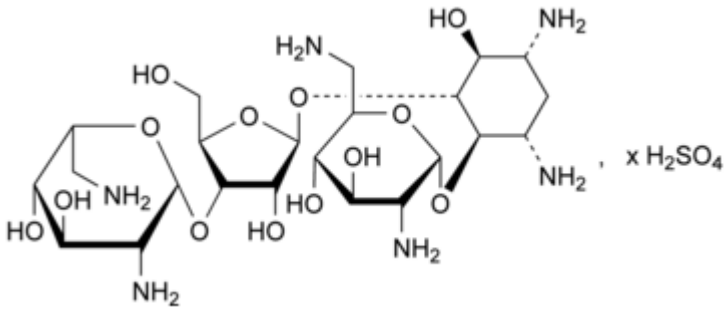
Parameter	Nomenclature and structure
Structural formula (neomycin B sulfate)	
Chemical family	Aminoglycoside

Table 2: Key physicochemical properties of the active constituent neomycin

Parameter	Physicochemical property
Colour	White or yellowish-white, hygroscopic
Physical state	Powder
Specific rotation	+53.5 to +59.0 (dried substance)
pH	5.0 to 7.5 in a water solution containing 33 mg of neomycin per mL
Solubility in water	Very soluble in water, very slightly soluble in alcohol, practically insoluble in acetone

The APVMA has confirmed that the sources of neomycin (as the sulfate) as an active constituent for use in veterinary products within the scope of the reconsideration comply with standards set by the European Pharmacopoeia, British Pharmacopoeia or United States Pharmacopoeia.

Products

There are currently 25 registered products containing neomycin (sulfate) as an active constituent, with a further 6 vaccine products containing neomycin as a preservative. However, only 9 registered products fall within the scope of the reconsideration (oral, injectable or intramammary products) of neomycin, which are listed in Table 3 below.

Table 3: Currently registered products containing neomycin within scope of the reconsideration

Registration number	Product name	Holder	Formulation type
36026	Scourban Oral Anti-Diarrhoeal Suspension	Elanco Australasia Pty Ltd	Oral solution/suspension
49788	Scour-X Oral Anti-Diarrhoeal Suspension	Ausrichter Pty Ltd	Oral solution/suspension
52782	CCD Neomycin (Neomycin Sulphate Water Soluble Powder)	Ccd Animal Health Pty Ltd	Oral powder
67805	Abbeyneo Antibiotic Feed Additive	Abbey Laboratories Pty Ltd	Oral powder
46414	Neo-Sulcin Scour Tablets	Jurox Pty Ltd	Oral tablet
36237	Jurox Neomycin Sulfate Injection	Jurox Pty Ltd	Parenteral liquid/solution/suspension
37241	Neomycin Penicillin 100/200 Aqueous Suspension for Intramuscular Injection	Intervet Australia Pty Ltd	Parenteral liquid/solution/suspension
38696	Special Formula 17900 Forte-V Lactating Intramammary Antibiotic Suspension	Zoetis Australia Pty Ltd	Intramammary suspension
49851	Mastalone Intramammary Suspension or Lactating Cows	Zoetis Australia Pty Ltd	Intramammary suspension

The formulation of the products, stability, shelf life, storage conditions and associated label directions have been considered and the APVMA is satisfied that these remain appropriate, except for the:

- stability and shelf life of products where an interim shelf life applies
- storage statements on the labels of products, which should be updated to reflect current labelling practice. In particular, the statements regarding storage under freezing conditions for liquid products in Table 3 and statements regarding protection from light for all products in Table 3 should be updated.

The active constituent is expressed on product labels as either neomycin (as neomycin sulfate) or neomycin sulfate. The current standard for the expression of the active is to specify the concentration of neomycin (as neomycin sulfate). This expression provides information on the concentration of the active moiety (the neomycin itself) and allows for easier comparison with other forms of neomycin, such as neomycin hydrochloride, in the event that such products were registered. It is further noted that this convention is widely used for other antibiotics, such as gentamicin sulfate and by other regulatory agencies such as the UK Veterinary Medicines Directorate.

Recommendations

The APVMA remains satisfied with respect to the chemistry and manufacturing aspects of the safety and efficacy criteria for neomycin products and notes that the expression of the active constituent on product labels should be amended to neomycin (as neomycin sulfate).

Products subject to an interim shelf life should be required to provide stability data for assessment to allow the validity of the interim shelf to be confirmed and approved.

Storage statements on all product labels should be revised to meet current practice regarding protection from freezing temperatures for liquid products and protection from light for all products. This includes the addition of ‘do not freeze’ statements on liquid products and ‘protect from light’ statements on all products where low temperature stability data and photostability data have not been previously provided and assessed to demonstrate that these statements are not required.

Human health

Although human health including toxicology and worker health and safety was not in the scope of the reconsideration, the APVMA has conducted a review of the available information.

Evaluation of toxicology

The toxicity of neomycin is well characterised. Neomycin is used as a human therapeutic agent in certain circumstances however, it is associated with a risk of ototoxicity and kidney damage. On a conservative basis, the point of departure for assessment of occupational health and safety is the 6 mg/kg bw/day, the no observed adverse effect level (NOAEL) upon which the acceptable daily intake (ADI) is set. This NOAEL was set on the basis of ototoxicity observed at the next higher dose in a 3-month dietary study in guinea pigs. A margin of exposure of at least 100 is considered suitable, including 10x for interspecies differences and 10x for intraspecies difference. This is considered a very conservative basis for risk assessment, particularly given that doses of up to 12 g per day (equating to approximately 150 mg/kg bw/day) are approved for oral administration to adults (in the US).

The oral absorption of neomycin is very low, with most of the orally administered neomycin being excreted unchanged in the faeces. It is estimated that around 0.6% of orally administered neomycin is available systemically. Dermal absorption of neomycin is extremely limited (James *et al* 1970).

Poisons scheduling

As shown in Table 4 below, neomycin is currently listed as a schedule 4 poison in the Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard).

Table 4: Scheduling of neomycin in the Poisons Standard

Schedule	Title	Description
Schedule 4	Prescription only medicines and prescription animal remedies	Substances, the use or supply of which should be by or on the order of persons permitted by state or territory legislation to prescribe and should be available from a pharmacist on prescription.

Worker health and safety

The exposure to workers dispensing neomycin products is dependent on the formulation and use pattern associated with each of the individual product types. The product formulations which fall within the scope of this reconsideration have been considered below.

Feed additive powder formulations

Neomycin is present in powder formulations at 600 mg/kg product for use as feed additives for pigs, poultry and cattle. The powders are mixed with a small quantity of feed before blending into larger quantities.

The recommended dose rate is 8 to 22 mg neomycin/kg bw/day. Medicated feed is to be used for 3 to 5 days for the treatment of bacterial scours in poultry, pigs and cattle.

Powdered feed additives are mixed with feed prior to blending into larger quantities. There is potential for inhalational exposure to the neomycin powder, as well as limited dermal exposure during mixing of the feed. Given the medicated feed is to be provided for 3 to 5 days, it is considered possible that the entire batch of feed may be mixed on a single occasion.

Maximum exposure is considered likely to be associated with the treatment of a large number of cattle, based on quantity of neomycin required for their average bodyweight. At the maximum dose of 22 mg neomycin/kg bw/day, adult cattle may receive up to 15.4 g of neomycin. It is considered possible that an individual may mix feed for 5 days of treatment on a single occasion. The maximum number of cattle considered likely to be treated with this treated food is 200, leading to a possible maximum exposure of 15.4 kg on a single day (15.4 g × 5 day × 200 animals).

The majority of exposure resulting from mixing treated feed is considered likely to result from inhalation of released dust particles, with dermal exposure considered to be minimal. Neomycin powder formulations are likely to have at least 75% of the formulation in the inhalable fraction with particles <10 µm. Based on estimates of unit exposure derived from the properties of the dry flowable powder of 19.7 µg/kg active constituent, handing 15.4 kg would lead to a total exposure of 304 µg per day. Assuming an inhalation absorption factor of one, and a bodyweight of 80 kg, this would lead to a total daily exposure of 3.8 µg/kg bw/day.

The systemic dose achieved from the oral NOAEL is estimated to be 0.036 mg/kg bw/day (0.6% of 6 mg/kg bw/day). This estimated exposure of 3.8 µg/kg bw/day, or 0.0036 mg/kg bw/day, is only 10-fold lower than the point of departure. However, it is noted that neomycin is used therapeutically in humans, with systemic doses achieved during therapeutic use of several orders of magnitude higher than the worst-case dose anticipated during occupational use. On this basis, personal protective equipment to reduced systemic exposure is not required. However, based on good operational practice, the use of a dust mask when handling powder formulations is recommended. It is also considered that there is a potential for powdered formulations to irritate the eyes based on their physical properties. The statement *'May irritate the eyes. Avoid contact with eyes'* is recommended, and it is also recommended that the safety directions *'When using the product, wear a disposable dust mask covering the nose and mouth'* and *'Wash hands after use'* be included on the product labels for feed additive powder formulations.

Oral suspension and tablets

Neomycin sulfate is present in oral suspension formulations in combination with a number of other substances to assist in rehydration for the treatment of diarrhoea and gastroenteritis and scour/pneumonia complex in a range of species. Products are administered orally at 2 mL/3 kg in small animals, and 30 mL (54 mg neomycin sulfate) per 25 kg in calves and horses, given twice daily. Treatment is given for a 3- to 5- day period.

A tablet formulation is also available containing 250 mg neomycin sulfate/tablet, to be dose at one tablet per 35 kg bw, administered twice daily.

As these products are administered directly, there is limited potential for inhalation exposure, and dermal exposure is also anticipated to be negligible.

It is recommended that the safety direction *'Wash hands after use'* be included on the product labels for both the oral suspension and tablet formulations for direct treatment of animals.

Solution for injection

Neomycin sulfate is available as solution for injections, either as the sole active constituent or in combination with procaine penicillin. In horses, cattle, sheep and pigs, neomycin sulfate is administered at up to 5 mg/kg bw, either 2 or 3 times per day. In dogs and cats, it is administered at 10 mg/kg bw daily, in divided doses.

There is not anticipated to be dermal exposure related to the administration of an injectable solution to animals. The highest risk associated with these products is that associated with needle stick injury. Additional precautions to minimise the risk of needle stick injury, such as the use of protective gloves, are not considered necessary, given the use of neomycin as a human therapeutic.

It is recommended that the safety direction: *'Wash hands after use'* be included on the product labels for injectable formulations for direct treatment of animals.

Intramammary preparation

A number of products containing neomycin sulfate in combination with other antibiotics are available for the treatment of mastitis in cattle. Exposure from the use of these products will be primarily dermal, and systemic exposure to those administering the preparations is anticipated to be below levels of concern.

It is recommended that the safety direction: *'Wash hands after use'* be included on the product labels for intramammary preparations.

Recommendations

Although human health including worker health and safety were not formally included in the scope of this reconsideration, the following first aid instructions and safety directions are recommended for neomycin formulations. These recommendations will be included in the First Aid and Safety Direction Handbook.

First aid instructions

Table 5 shows the entry for neomycin in the Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals (the FAISD Handbook).

Table 5: FAISD Handbook – existing entry

Substance	Notes	First aid instructions	Warning statements and general safety precautions
Neomycin		a	

The code 'a' in Table 5 above refers to the following first aid instruction:

> If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 13 11 26, New Zealand 0800 764 766.

The first aid instructions entry is considered appropriate and should remain unchanged.

Safety directions – Oral (liquid), oral (tablet), injectable and intramammary formulations

Table 6 below shows new entries to the FAISD Handbook for neomycin.

Table 6: FAISD Handbook – new entry

Substance	Formulation	Statement codes
Neomycin	AL, OI, PA, TB	351

The statement codes translate into the following safety directions:

Table 7: FAISD Handbook – new entry, translation of statement codes to safety directions

Safety directions	Code
Wash hands after use	351

The following safety directions should be added to supported oral (liquid), oral (tablet), injectable and intramammary formulations containing neomycin:

> Wash hands after use.

Powder formulations

Table 8 below shows new entries to the FAISD Handbook statement codes for powder formulations of neomycin.

Table 8: FAISD Handbook – new entry

Substance	Formulation	Statement codes
Neomycin	PD	160 162 210 162 279 283 290 306 351

The statement codes translate into the following safety directions:

Table 9: FAISD Handbook – new entry, translation of statement codes to safety directions

Safety directions	Code
May irritate the eyes.	160 162
Avoid contact with eyes.	210 162
When using the product, wear a disposable dust mask covering the nose and mouth.	279 283 290 306
Wash hands after use.	351

The following safety directions should be added to supported powder formulations containing neomycin:

> May irritate the eyes. Avoid contact with eyes. When using the product, wear a disposable dust mask covering the nose and mouth. Wash hands after use.

Residues and trade

Current residues definition and maximum residue limits

The current residue definition for neomycin in the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023 (MRL Standard) is expressed as 'inhibitory substance, identified as neomycin'.

Current entries in Table 1 of the MRL Standard for neomycin are summarised in Table 10 below:

Table 10: Entries for neomycin in Table 1 of the MRL Standard

Compound	Food			MRL (mg/kg)
Neomycin				
	PE	0112	Eggs	T0.5
	MO	0098	Kidney of cattle, goats, pigs and sheep	T10
	MO	0099	Liver of cattle, goats, pigs and sheep	T0.5
	MF	0100	Mammalian fats {except Milk fats}	T0.5
	MM	0095	Meat (mammalian)	T0.5
	ML	0106	Milks	T1.5
			Poultry kidney	T10
			Poultry, liver	T0.5
	PM	0110	Poultry meat	T0.5

There are no entries for neomycin in either Table 4 or Table 5 of the MRL Standard.

Reconsideration of the residue definition for neomycin

The current Australian residues definition for neomycin is expressed as 'Inhibitory substance, identified as neomycin'. For the detection of neomycin, instrumental methods are now available in addition to microbiological assay methods which were available when the current residue definition was established. It is understood that contemporary chromatography methods for analysis of neomycin have several advantages in contemporary practice over microbiological method in terms of precision, accuracy, and shorter testing time.

As neomycin is subject to negligible metabolism in animals, it is considered appropriate to align the Australian residue definition (marker compound) of neomycin to that established by Codex as 'neomycin'. The microbiological and instrumental methods are considered comparable for the quantification of neomycin,

therefore residues data which utilised the microbiological method are considered relevant to the proposed residue definition of ‘neomycin’.

Residues risk assessment

The available residues data that is relevant to currently approved use patterns for neomycin in food producing species (cattle, sheep, pigs and poultry) are considered in this section. Horses are not generally considered a food producing species in Australia, however appropriate label instructions to manage potential residue concerns in horses will be considered.

The residues risk assessment is aimed at addressing consumer safety, and for setting appropriate withholding periods (WHP), re-treatment intervals and export slaughter intervals (ESI) on product labels. It is critical that the APVMA have access to residues data that was generated utilising the specific formulation of the product registration in question. This is consistent with the APVMA residue guidance and VICH guidelines that clearly states the test product employed in the study should be representative of the commercial formulation.

The use of neomycin in cattle, horses, pigs, poultry and sheep are considered below, separated based on the routes of administration and products.

Solution for injection

There are 2 neomycin products registered for injection into cattle, sheep, pigs and horses. These are:

- registered product number 36237, which contains 200 mg/mL neomycin sulfate
- registered product number 37241, which contains 100 mg/mL neomycin (as the sulfate) and 200 mg/mL procaine penicillin.

Product 36237

Residues data is not available for cattle, sheep, pig and horse tissues for this product. The available cattle, sheep and pig tissue studies involved a dose rate of 5 mg neomycin/kg bw (24 hrs apart for 3 days) (De Kleyne 1989a, 1989b, 1989c). This differs from label dose rate of 2 to 4 mg neomycin/kg bw (every 8 to 12 hours) for product 36237. It is also noted that the current meat withholding period of 10 days was not addressed in this study (sampling from 28 days). A cattle milk residue study is available for a similar formulation (Barbiers *et. al*. 1965), but it involved a dose rate of 10 mg/kg bw, which is higher than the label dose rate of 2 to 4 mg/kg for this product and is therefore not considered relevant to this label use.

In the absence of cattle tissue, cattle milk, sheep tissue and pig tissue residue data addressing this product formulation and use patterns, there is insufficient data to enable a robust assessment of the residue depletion profile for this formulation when administered to cattle, sheep and pigs via injection; and a WHP, re-treatment interval and ESI cannot be determined. The use of product 36237 in cattle, sheep and pigs is therefore not supported.

The use of product 36237 in horses is supported from a residues perspective, provided the restraint 'DO NOT USE in horses that may be used for human consumption' is added to the label and the current meat WHP for horses is removed.

Product 37241

Cattle

Residues data is available for cattle tissues for this product (De Kleyne 1989a). Calves (n=16) were administered 3 doses of 5 mg neomycin/kg bw with 10 mg procaine penicillin/kg bw 24 hours apart via intramuscular injections. Animals were sacrificed (n=4) at 28, 42, 56 and 70 days after treatment and samples from fat, liver, kidney and muscle (inc. injection site) were collected for residues analysis. The limit of detections for neomycin in fat, liver, kidney and muscle were 0.10 mg/kg, 0.16 mg/kg, 0.16 mg/kg and 0.08 mg/kg, respectively.

Finite residues of penicillin were not detected in muscle, liver, kidney or fat at any time point (28 days to 70 days) and appropriate MRLs for penicillin (Benzyl G penicillin) are established in the MRL standard at *0.06 mg/kg for meat (mammalian) and edible offal (mammalian) and at *0.0015 mg/kg milk. Therefore, residue and trade aspects relating to penicillin are not discussed any further. For this product, WHP and ESI will be driven by neomycin which showed quantifiable residues in edible tissues.

At the first time-point, 28 days after treatment, the highest neomycin residue (HR) in liver was 1.19 mg/kg and residues generally declined to <LOD at 56- and 70-days post-treatment, aside from a single sample (out of 4 samples at each time-point) with residues of 0.17 mg/kg on day 70. At the first time-point (day 28), which is the closest time-point to the current meat WHP of 35 days, the HR for kidney samples was 7.31 mg/kg. Kidney was the target tissue noting higher finite residues of neomycin, when compared to liver, muscle and fat, at all time points including at the last time point of 70 days post treatment where residues were 0.62 to 3.52 mg/kg. Residues of neomycin in injection site muscle tissues were below the LOQ of 0.16 mg/kg in all samples taken at days 28, 42 and 56 (samples not analysed at day 70) except for one day 42 sample where a residue of 0.20 mg/kg was observed. Residues were below limit of determination for muscle (<0.08 mg/kg) and fat (<0.10 mg/kg) in all samples taken at days 28, 42, 56 and 70.

The appropriateness of the cattle commodity temporary MRLs for neomycin (10 mg/kg for kidney, 0.5 mg/kg for liver, 0.5 mg/kg for Mammalian fats [except Milk fat], 0.5 mg/kg for Meat (mammalian) for the registered critical use rate and associated WHPs (35 days) were assessed through statistical analysis of the neomycin residues depletion curves of the individual edible cattle tissues using the EMA Meat WT version.1.4 software.

Statistical analysis of the 95 percentile decline profile of neomycin residues indicated that a WHP of 42 days would comply with the current temporary kidney MRL of 10 mg/kg. On that basis, a 42-day WHP is considered necessary for cattle kidney to establish an Australian MRL at 10 mg/kg.

A WHP of 42 days, driven by the residues in the target tissue kidney, would require an MRL of 1.3 mg/kg for liver based on statistical analysis of the 95 percentile decline profile.

Residues in fat and muscle were below the limit of determination of 0.10 mg/kg and 0.08 mg/kg respectively at all time points (28, 42, 56 and 70 days). Therefore, MRLs at *0.1 mg/kg for cattle fat and *0.08 mg/kg for

cattle muscle are considered appropriate based on the available data for the supported use pattern with a 42-day meat WHP.

The following withholding period is recommended for the use of this product in cattle:

MEAT: Cattle: DO NOT USE less than 42 days before slaughter for human consumption.

The supported MRLs for neomycin in cattle tissues for this use are detailed in Table 11 below.

Table 11: Supported MRLs for neomycin in cattle tissues

Compound	Food	MRL (mg/kg)
Neomycin		
MF 0812	Cattle fat	*0.1
	Cattle muscle	*0.08
MO 1280	Cattle, kidney	10
MO 1281	Cattle, liver	1.3

Re-treatment interval (between courses)

The available residues data addressed one treatment course involving 3 consecutive injections, made one day apart, at 5 mg neomycin/kg bw and 10 mg procaine penicillin/kg bw. The approved label for registered product number 37241 does not carry a minimum retreatment interval between courses and the submitted trial does not include a re-treatment interval. A re-treatment interval between courses is considered important to prevent a second course being administered to the same animal before residues have declined as this may lead to residues in tissues above the recommended MRLs.

For neomycin residues in cattle kidney, the target tissue, finite residues (0.62 to 3.52 mg/kg) were observed at the last time point of 70 days post treatment. Statistical analysis at the 95 percentile of the decline profile indicates that after 365 days (12 months), residues will decline to 0.25 mg/kg, which is just above the limit of determination from the study of 0.16 mg/kg. It is considered that a 12-month re-treatment interval is required to manage the risk of unacceptable accumulation of neomycin residues between treatments in cattle.

The following restraint is recommended for the use of this product in cattle:

RESTRAINT: RE-TREATMENT INTERVAL

DO NOT RE-TREAT cattle for 12 months after the last dose in one course of treatment

Milk withholding period

Residues depletion data in milk is available (Anonymous 1973–79) for the product 37241 (containing neomycin and penicillin) however, the residue study is lacking in critical details that are required to determine the residue depletion profile in milk and ascertain whether the product meets the safety criteria and whether its use would present an undue risk to trade. Thus, the following withholding period is recommended for use of this product in cattle:

> MILK: DO NOT USE in lactating or pregnant cows where milk may be used or processed for human consumption

Export Slaughter Interval (ESI)

Noting the neomycin MRLs established by major export markets (see the 'Trade consideration' section below'), the ESI for neomycin in cattle should be based upon the time required for residues to decline to 7.2 mg/kg in cattle kidney and 0.5 mg/kg in cattle liver to prevent an undue risk to trade. The output of the Statistical analysis for the determination of an ESI for this use on cattle is shown below:

Statistical analysis at the 95 percentile of the decline profile indicated that a ESI of 50 days would allow residues to comply with the lowest international MRL for cattle kidney at 7.2 mg/kg.

Statistical analysis at the 95 percentile of the decline profile indicated that a ESI of 57 days would allow residues to comply with the lowest international MRL for cattle liver at 0.5 mg/kg.

Based on the available information, an ESI of 57 days will be required for neomycin residues to meet overseas standards and to comply with international MRLs.

The following trade advice statement is recommended for the use of this product in cattle:

> TRADE ADVICE: EXPORT SLAUGHTER INTERVAL
>
> EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 57 days for cattle before slaughter for export. Before using this product, confirm the current ESI from the manufacturer on 1800 033461 or the APVMA website (apvma.gov.au/residues).

Sheep

Residues data is available for sheep tissues for this product (De Kleyne 1989b). Sheep (n=17) were intramuscularly injected with 3 doses of 5 mg neomycin/kg bw, and 10 mg procaine penicillin/kg bw, 24 hours apart. Animals were sacrificed at 28, 42, 56 and 70 days after treatment and samples of edible tissues (injection site, muscle, liver, kidney, fat) were collected and analysed (using an agar-diffusion method). The method LOD for neomycin in fat, liver, kidney and muscle were 0.1, 0.2, 0.2 and 0.08 mg/kg, respectively.

Finite residues of penicillin were not detected in muscle, liver, kidney or fat at any time point (28 days to 70 days) and appropriate MRLs for penicillin (Benzyl G penicillin) are established in the MRL standard at *0.06 mg/kg for meat (mammalian) and edible offal (mammalian) and at *0.0015 mg/kg milk therefore

residue and trade aspects relating to penicillin are not discussed any further. For this product, WHP and ESI will be driven by neomycin which showed quantifiable residues in edible tissues in the study considered.

Neomycin residues in the injection site tissue, muscle and fat were <0.16, <0.08 and <0.10 mg/kg at the first 3 time-points and were not determined for the final time-point at day 70. For liver, only 2 samples had residues >LOD (0.2 mg/kg), 0.93 mg/kg (day 28) and 0.67 mg/kg (day 42). The HR was 1.75 mg/kg (day 28) for kidney samples and a general decline to the final time-point was seen with the HR at day 70 being 0.36 mg/kg.

The appropriateness of the sheep commodity temporary MRLs for neomycin (T10 mg/kg for kidney, T0.5 mg/kg for liver, T0.5 mg/kg for Mammalian fats [except Milk fat] and T0.5 mg/kg for Meat (mammalian) for the registered critical use rate and associated WHP (35 days) was assessed through statistical analysis of the residues depletion curves of the individual edible sheep tissues using the EMA Meat WT version.1.4 software.

Statistical analysis based on the submitted residues data indicated that the existing sheep kidney MRL of 10 mg/kg can be reduced to 2.4 mg/kg in conjunction with the current WHP of 35 days.

Statistical analysis based on the submitted residues data, indicated that the sheep liver MRL should be 1.4 mg/kg in conjunction with the current WHP of 35 days.

Residues in fat and muscle were below the limit of determination of 0.10 mg/kg and 0.08 mg/kg respectively at all time points (28, 42, 56 and 70 days). Therefore, MRLs at *0.1 mg/kg for sheep fat and *0.08 mg/kg for sheep muscle are considered appropriate based on the available data for the supported use pattern with a 35-day meat WHP.

The following withholding period is recommended for the use of this product in sheep:

MEAT: Sheep: DO NOT USE less than 35 days before slaughter for human consumption.

The supported MRLs for neomycin in sheep tissues for this use are detailed in Table 12 below:

Table 12: The supported MRLs for neomycin in sheep

Compound	Food	MRL (mg/kg)
Neomycin		
MF 0822	Sheep fat	*0.1
MO 1288	Sheep, kidney	2.4
MO 1289	Sheep, liver	1.4
	Sheep muscle	*0.08

Re-treatment interval (between courses)

The available data addressed one treatment course involving 3 consecutive injections, made one day apart, at 5 mg neomycin/kg bw and 10 mg procaine penicillin/kg bw. The approved label for the registered product 37241 does not carry a minimum retreatment interval between courses and the submitted trial does not include a re-treatment interval. A re-treatment interval between courses is considered important to prevent a second course being administered to the same animal before residues have declined as this may lead to residues in tissues above the recommended MRLs.

For neomycin residues in sheep kidney, the marker tissue, finite residues (0.28 to 0.36 mg/kg) were observed at the last time point of 70 days post treatment. Statistical analysis at the 95 percentile of the decline profile indicates that after 133 days (~4 months), residues will decline to below the limit of determination from the study of 0.20 mg/kg. It is considered that a 4-month re-treatment interval should manage the risk of unacceptable accumulation of neomycin residues between courses in sheep.

The following restraint is recommended for the use of this product in sheep:

> RESTRAINT: RE-TREATMENT INTERVAL
>
> DO NOT RE-TREAT sheep for 4 months after the last dose in one course of treatment.

Milk withholding period

Residue depletion studies in sheep milk are not available to estimate residues of neomycin in sheep milk. Therefore, the following restraint is recommended for use of this product in sheep to prevent consumption of milk.

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

Export slaughter interval

Noting the neomycin MRLs established by major export markets (see the ‘Trade consideration’ section below), the ESI for neomycin in sheep should be based upon the time required for residues to decline to 0.5 mg/kg in sheep liver to prevent an undue risk to trade.

For sheep liver, based on the results of the residues study which found a residue of 0.93 mg/kg in sheep liver at 28 days after treatment, a residue of 0.67 mg/kg at 42 days after treatment but residues below the limit of determination at 0.2 mg/kg at 56 days after treatment, it is considered appropriate to establish an ESI of 56 days for sheep for this product.

The following trade advice statement is recommended for the use of this product in sheep:

> TRADE ADVICE: EXPORT SLAUGHTER INTERVAL
>
> EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 56 days for sheep before slaughter for export. Before using this product, confirm the current ESI from the manufacturer on 1800 033461 or the APVMA website (apvma.gov.au/residues).

Pigs

Residues data is available for pig tissues for this product (De Kleyne 1989c). Pigs (n=16) were administered 3 injections of 5 mg neomycin/kg bw (and 10 mg procaine penicillin/kg bw) 24 hours apart. Animals (n=4) were sacrificed and tissue samples (injection site, muscle, liver and kidney) taken for analysis at day 28, 42, 56 and 70 after treatment. The LOD of the method for neomycin in fat, liver, kidney and muscle was 0.1, 0.2, 0.2 and 0.08 mg/kg, respectively.

Finite residues of penicillin were not detected in muscle, liver, kidney or fat at any time point (28 days to 70 days) and appropriate MRLs for penicillin (Benzyl G penicillin) are established in the MRL standard at *0.06 mg/kg for meat (mammalian) and edible offal (mammalian) and at *0.0015 mg/kg milk therefore residue and trade aspects relating to penicillin are not discussed any further. For this product, the WHP and ESI will be driven by neomycin which showed quantifiable residues in edible tissues in the study considered.

Residues of neomycin were <LOD for the injection site, muscle and fat. The HR in liver and kidney were 1.02 (day 28) and 5.96 mg/kg (day 28). Residues in liver declined to <LOD (0.2 mg/kg) at day 56 onwards. Residues in kidney declined to <LOD (0.2 mg/kg) at the final time-point (day 70).

Neomycin residues in fat and muscle were below the limit of determination of 0.10 mg/kg and 0.08 mg/kg respectively at all time points (28, 42, 56 and 70 days). While finite residues were observed in pig liver at days 28 and 42, and in pig kidney at days 28, 42 and 56, residues in liver and kidney were below the limit of determination of 0.20 mg/kg at the last time point of 70 days. Given that the current pig WHP is 100 days, finite levels of neomycin residues are not expected in any tissue when label directions are followed. Therefore, MRLs at *0.2 mg/kg for pig liver and pig kidney, *0.1 mg/kg for pig skin/fat and *0.08 mg/kg for pig muscle are considered appropriate based on the available data for the supported use pattern with a 100-day meat WHP.

The following withholding period is recommended for the use of this product in pigs:

MEAT: Pigs: DO NOT USE less than 100 days before slaughter for human consumption.

The supported MRLs for neomycin in pig tissues for this use are detailed in Table 13 below.

Table 13: The supported MRLs for neomycin in pig tissues

Compound	Food	MRL (mg/kg)
Neomycin		
	Pig fat/skin	*0.1
	Pig muscle	*0.08
MO 1284	Pig, kidney	*0.2
MO 1285	Pig, liver	*0.2

Re-treatment interval (between courses)

The available residues data addressed one treatment course involving 3 consecutive injections, made one day apart, at 5 mg neomycin/kg bw and 10 mg procaine penicillin/kg bw. The approved label for registered product 37241 does not carry a minimum retreatment interval between courses and the submitted trial does not include a re-treatment interval. A re-treatment interval between courses is considered important to prevent a second course being administered to the same animal before residues have declined as this may lead to residues in tissues above the recommended MRLs.

For neomycin residues in pig kidney, the target tissue, finite residues (0.39 to 0.44 mg/kg) were observed at 56 days post treatment but residues were below the limit of determination of the study (0.2 mg/kg) at 70 days (10 weeks) post treatment. It is considered that a 10-week re-treatment interval should adequately manage the risk of unacceptable accumulation of neomycin residues between treatments in pigs.

The following restraint is recommended for the use of this product in pigs:

> RESTRAINT: RE-TREATMENT INTERVAL
>
> DO NOT RE-TREAT pigs for 10 weeks after the last dose in one course of treatment.

Export slaughter interval

An ESI for neomycin in pigs should be the same as the meat WHP as the recommended neomycin MRLs are lower than those established overseas. A 100-day ESI is supported for this use in pigs.

The following trade advice statement is recommended for the use of this product in pigs:

> TRADE ADVICE: EXPORT SLAUGHTER INTERVAL
>
> EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 100 days for pigs before slaughter for export. Before using this product, confirm the current ESI from the manufacturer on 1800 033461 or the APVMA website (apvma.gov.au/residues).

Horses

Residues data is not available for horse tissues for this product. The use of neomycin in horses is supported from a residues perspective, provided the restraint ‘DO NOT USE in horses that may be used for human consumption’ is added to the label, and the current meat WHP for horses be removed.

Feed additive powder formulation

There is one neomycin product registered for injection oral administration in feed to cattle, pigs and poultry. This is registered product number 67805, which contains 600 g/kg neomycin (as sulfate).

Product 67805

Resides data is not available for cattle tissues, cattle milk, pig tissues and poultry for this feed additive product.

The available oral in feed trial for cattle tissue involved a combination of active ingredients, neomycin and terramycin, and a dose rate of 10 mg neomycin/kg bw (Hawbaker & Hart 1967a). This is similar to the lowest label dose rate of 8 mg/kg bw, but lower than the highest label dose rate of 22 mg/kg bw. The dosage duration (once daily for 10 days) in the trial was longer than the label duration of 3 to 5 days. It is also noted that the available study only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.18 and 0.38 mg/kg depending on tissue and sampling time were higher than the limits of quantification of contemporary methods for neomycin.

There is no available oral in feed trial for cattle milk for the active ingredient neomycin.

The available neomycin oral in feed trial for pig tissue involved a dose rate of 10 mg neomycin/kg bw, which is similar to the lowest label dose rate of 8 mg/kg bw but lower than the highest label dose rate of 22 mg/kg bw (Liu *et. Al.* 1981). The dosage duration (once daily for 10 days) in the trial was longer than the label duration of 3 to 5 days while tissues samples were only collected at 3 and 5 days after treatment and not at the meat WHP of 20 days. It is also noted this study only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.16 and 0.31 mg/kg depending on tissue were higher than the limits of quantification of contemporary methods for neomycin. There were 3 additional oral in feed trials available for pig tissues involving neomycin co-formulated with terramycin or licomycin (Davis & Hart 1966, Davis & Hart 1967, Liu *et. Al.* 1981), which were not considered relevant to product 67805.

Three chicken studies and one turkey study addressed oral in feed administration that were generated using neomycin in combination with terramycin. These trials involved administration of a ration containing 140 g neomycin/tonne (140 ppm) and 200 g terramycin/tonne (200 ppm) for 21 consecutive days (Bentley & Williams 1966, Newkirk & Hart 1966a, Newkirk & Hart 1966b, Newkirk & Hart 1966c). This dosage regime is significantly different to the dosage regime which is registered for poultry (8 to 22 mg neomycin/kg bw for 3 to 5 days). It is also noted that these studies predominantly involved only 3 birds per sampling time point, half the number of 6 birds per sampling time which is the contemporary standard for poultry trials specified in APVMA and VICH guidance.

A fourth study relevant to oral in feed administration to chickens involved administration of a ration containing 154 or 770 ppm of neomycin for the first 3 days of their life (Liu 1984), which again is significantly different to the registered dosage regime of product 67805. This study involved the sampling of 45 chicks (treated as day olds) per timepoint, but the tissue samples were pooled for analysis and is not considered to be relevant to current label uses.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and the feed additive product, there is insufficient residues data to enable a robust assessment of the residue depletion profile for this neomycin products when administered to cattle, pigs and poultry via treated feed; and a WHP, re-treatment interval and ESI (for cattle and pig uses) cannot be determined. The use of product 67805 in cattle, pigs and poultry is therefore not supported.

Oral suspension formulations

There are 2 neomycin products registered for oral solution administration to cattle (including calves) and horses. These are registered product numbers 36026 and 49788, which contain 54 mg/30 mL neomycin sulfate and other active ingredients.

Products 36026 and 49788

Resides data is not available for cattle tissues, cattle milk and horse tissues for these oral suspension products.

The 3 available residue depletion studies relevant to oral solution (drench) administration of neomycin to cattle involved single dose at 10 mg/kg bw for 5 to 10 consecutive days (Newkirk & Hart 1966d, Hawbaker & Hart 1967b, Hawbaker & Hart 1967c). The formulations used in these studies and the dosage regime is different to that registered for products 36026 and 49788 (2.16 mg/kg twice daily for a minimum of 5 days). It is also noted that these 3 studies only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.17 and 0.5 mg/kg, which is higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and these oral suspension products, there is insufficient residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to cattle via oral solution; and a WHP, re-treatment interval and ESI cannot be determined. The use of products 36026 and 49788 in cattle is therefore not supported.

The use of neomycin on horses is supported from a residues perspective, provided the restraint ‘DO NOT USE in horses that may be used for human consumption’ is added to the label, and the current meat WHPs for horses be removed.

Oral solution as water additive

There is one neomycin product registered for oral in water administration for poultry. This is registered product number 52782, which contains 600 g/kg neomycin as sulfate.

Product 52782

Resides data is not available for poultry for this oral in water administration product.

The available residue studies relevant to oral in water administration to broiler chickens and ducks address a dose rate of 30 mg neomycin/kg bw administered for 7 or 21 consecutive days for chickens and ducks respectively (Newkirk & Urban 1966, Ibayashi *et al*. 1994). This dosage regime is significantly different to the maximum dosage regime which is registered for poultry (100 mg neomycin/kg bw for 3 to 5 days). It is also noted that the chicken and duck studies involved only 3 birds per sampling time point, half the number of 6 birds per sampling time which is the contemporary standard for poultry specified in APVMA and VICH guidance.

The available studies relevant to oral in water administration to turkeys address a dose rate of 22 mg neomycin/kg bw administered for 5 consecutive days, but not address the maximum registered dose rate of 100 mg neomycin/kg bw (Marren 1995). It is also noted that the limit of determination of 0.5 mg/kg in this study was higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the treatment regimens between the residue trials discussed above and this product, and because the available poultry studies do not meet contemporary standards with regards to sample number and limits of quantification, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to all poultry via water; and a WHP and re-treatment interval cannot be determined. The use of product 52782 in poultry is therefore not supported.

Oral tablet formulation

There is one neomycin product registered for tablet administration to cattle, including calves, and horses. This is registered product number 46414, which contains the antibiotics neomycin (250 mg/tablet), sulfadimidine (750 mg/tablet) and sulfadiazine (750 mg/tablet), hyoscine and vitamins.

Product 46414

Resides data is not available for cattle tissues, cattle milk and horse tissues for this oral tablet product.

The 2 available cattle bolus trials use a different formulation and involved a dose rate of 10 mg neomycin/kg bw (Hawbaker & Hart 1966, Hawbaker & Hart 1967d), which is higher than the label dose rate of 7.14 mg neomycin/kg bw for product 46414. It is also noted that the 2 available studies only addressed 3 animals per time point (which is lower than contemporary requirements) and that the limits of determination which ranged between 0.25 and 0.37 mg/kg depending on tissue were higher than the limits of quantification of contemporary methods for neomycin.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and this oral tablet product, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin for this formulation when administered to cattle via a tablet; and a WHP, re-treatment interval and ESI cannot be determined. The use of product 67805 in cattle is therefore not supported.

The use of neomycin on horses is supported from a residues perspective, provided the restraint ‘DO NOT USE in horses that may be used for human consumption’ is added to the label, and the current meat WHP for horses be removed.

Intramammary preparations

There are 2 neomycin products registered for intramammary administration to lactating cows. These are:

- registered product number 38696, which contains neomycin, novobiocin and dihydrostreptomycin
- registered product number 49851, which contains neomycin, oleandomycin and oxytetracycline.

Product 38696

Residues data is not available for cattle tissues and cattle milk for this product.

While residues data generated using a combination of neomycin and lincomycin is available, residues data for neomycin co-formulated with novobiocin and dihydrostreptomycin were not available. In one milk study (Deluyker *et al*. 1996) and a tissue study (Nouws *et al*. 1997), neomycin was administered at 100 mg neomycin in each of the 4 quarters, while in the other milk study (Nouws *et al*.1994) neomycin was administered at 200 mg neomycin in 2 of the 4 quarters. These treatment regimens differ from the registered use pattern involving administration at 150 mg neomycin in up to 4 quarters of the udder.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and this product, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to cattle via an intramammary route; and WHPs, re-treatment interval and ESI cannot be determined. The use of product 38696 in lactating cows is therefore not supported.

Product 49851

Residues data is not available for cattle tissues and cattle milk for this product.

While residues data generated using a combination of neomycin and lincomycin is available, residues data for neomycin co-formulated with oleandomycin and oxytetracycline were not available. In one milk study (Deluyker *et al*. 1996) and the tissue study (Nouws *et al*. 1997), neomycin was administered at 100 mg neomycin in each of the 4 quarters for 3 days, which does address this registered dose rate. Further, the milk study however involved sampling up to 120 hours (5 days) after the last infusion and therefore does not address the current milk withholding period of 7 days. Similarly for tissues, the study addressed sampling times of one, 7, 14 and 21 days after the last infusion and does not address the current meat withholding period of 30 days.

Due to differences in the test formulation and treatment regimens between the residue trials discussed above and this product, there is insufficient relevant residues data to enable a robust assessment of the residue depletion profile for neomycin when administered to cattle via an intramammary route; and WHPs, re-treatment interval and ESI cannot be determined. The use of product 49851 in lactating cows is therefore not supported.

Trade considerations

Commodities of animal origin, such as meat, offal and dairy products are considered to be major export commodities. Residues in these commodities resulting from the veterinary uses of neomycin may have the potential to unduly prejudice international trade. Cattle, pig, sheep, goat and poultry tissues, cattle dairy product, and eggs are indicated as major Australian export food commodities. The significant export markets for Australian beef, sheep, pig and offal are listed in the Agricultural Data Guidelines – Pesticides: Overseas trade (Part 5B).

The MRLs in Table 14 have been established in major trading markets for meat, milk, eggs and offal products.

Table 14: Neomycin MRLs in some of Australia's major trading markets for animal commodities

Commodity	Neomycin MRLs (mg/kg)						
	Australia (current)	Australia (proposed)	CODEX[1]	USA[2]	EU[3]	Japan[4]	Korea[5]
	Inhibitory substance, identified as neomycin	Neomycin	Neomycin	Neomycin	Neomycin B	Neomycin B	
Cattle tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney 10 Muscle *0.08 Fat *0.1 Liver 1.3	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Kidney 9 Liver 5.5 Muscle 0.5 Fat 0.5	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Milk	Milk T1.5	Not supported	Milk 1.5	Milk 0.15	Milk 1.5	Milk 2	Milk 0.5
Sheep tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney 2.4 Muscle *0.08 Fat *0.1 Liver 1.4	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Fat 0.5 Kidney 9 Liver 5.5 Muscle 0.5 Milk 1.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5

Commodity	Australia (current)	Australia (proposed)	CODEX[1]	USA[2]	EU[3]	Japan[4]	Korea[5]
	Inhibitory substance, identified as neomycin	Neomycin	Neomycin	Neomycin	Neomycin B	Neomycin B	
Pig tissues	Kidney T10 Liver T0.5 Mammalian fats {except Milk fat} T0.5 Meat (mammalian) T0.5	Kidney *0.2 Muscle *0.08 Fat *0.1 Liver *0.2	Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Kidney 7.2 Liver 3.6 Muscle 1.2 Fat 7.2	Fat/skin 0.5 Kidney 9 Liver 5.5 Muscle 0.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Poultry	Kidney T10 Liver T0.5 Meat T0.5	Not supported	Chicken/duck/turkey: Kidney 10 Muscle 0.5 Fat 0.5 Liver 0.5	Turkeys: Kidney 7.2 Liver 3.6 Muscle 1.2	Fat/skin 0.5 Kidney 9 Liver 5.5 Muscle 0.5	Muscle 0.5 Fat 0.5 Liver 0.5 Kidney 10 Edible offal 10	Chicken/duck/turkey: Kidney 10 Liver 0.5 Muscle 0.5 Fat 0.5
Eggs	T0.5	Not supported	Eggs 0.5		Eggs 0.5	Eggs 0.5	Poultry egg 0.5

Export of treated produce containing finite (measurable) residues of neomycin may pose a risk to Australian trade in situations where (i) no residue tolerance (import tolerance) is established in the importing country or (ii) where residues in Australian produce are likely to exceed a residue tolerance (import tolerance) established in the importing country. An Export Slaughter Interval (ESI) can help manage the potential risk to trade in meat and offal arising from the use of products containing neomycin. As stated in the APVMA labelling code for veterinary products, trade advice statements such as ESIs are required on product labels for use in or on cattle, pigs or sheep.

[1] Food and Agriculture Organisation of the United Nations (FAO), 2024. *Codex online databases – CODEXALIMENTARIUS FAO-WHO*, FAO website.

[2] Electronic Code of Federal Regulations (eCFR), 2024. *Title 21, Chapter I, Subchapter E, Part 556, Subpart B – Specific Tolerances for Residues of Approved and Conditionally Approved New Animal Drugs*, eCFR website.

[3] EUR-Lex, 2023. *Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin*, EUR-Lex website.

[4] Japan Food Chemical Research Foundation (JPCRF), 2024. *List of limit amounts of pesticides, veterinary drugs, and feed additives remaining in food*, JPCRF website.

[5] Korean Ministry of Food and Drug Safety, 2024. *Veterinary Drugs MRLs*, Ministry of Food and Drug Safety website.

ESIs have not previously been established for currently registered neomycin products. However, consideration of appropriate ESIs are required for cattle, sheep and pig uses of neomycin to bring the trade advice statements on product labels up to contemporary standards and to prevent an undue risk to international trade.

For cattle fat and muscle, the recommended neomycin MRLs are lower than those established overseas. For cattle kidney, the recommended MRL at 10 mg/kg, is higher than the MRL established in the USA at 7.2 mg/kg. For cattle liver, the recommended MRL at 1.3 mg/kg is higher than that established by Codex, Japan and Korea at 0.5 mg/kg. The ESIs determined for cattle products are therefore based upon the time required for residues to decline to 7.2 mg/kg in cattle kidney and 0.5 mg/kg in cattle liver to prevent an undue risk to trade.

For sheep fat, kidney and muscle, the recommended neomycin MRLs are lower than those established overseas. For sheep liver, the recommended MRL at 1.4 mg/kg is higher than that established by Codex, Japan and Korea at 0.5 mg/kg. The ESIs determined for sheep products are therefore based upon the time required for residues to decline to 0.5 mg/kg in sheep liver to prevent an undue risk to trade.

For pig fat, kidney, liver and muscle, the recommended neomycin MRLs are lower than those established overseas. The ESIs determined for injectable sheep products above can therefore be equal to the meat WHP.

Dietary exposure assessment

The following health standards currently established in the APVMA lists for acceptable daily intakes for agricultural and veterinary chemicals are considered to be appropriate.

Table 15: Neomycin MRLs in some of Australia's major trading markets for animal commodities

Compound	Dietary Standard, mg/kg bw		No Observable Adverse Effect Level (NOaEL), mg/kg bw	Uncertainty factor	Reference (APVMA/OCS/JMPR, date)
Neomycin	ADI	0.06	6 (JECFA 96)	100	28/2/1986, OCS
	ARfD	Not established by APVMA or JECFA			

JECFA estimated dietary intake

The APVMA utilises the JECFA approach to MRL-setting where chronic exposure to total residues is estimated by multiplying the components of the conservative JECFA food basket (consisting of 300 g muscle, 100 g liver, 50 g kidney and 50 g fat) by the 'median residue' in each food (muscle, liver, kidney,

skin/fat) at a specified sampling time, and summing the total residues to determine the 'estimated daily intake' (EDI)[6]. These values are shows in Table 16 below.

Table 16: Estimated daily intake for neomycin residues

Edible tissue	MRL (mg/kg)#	Ratio of marker residue to total residues *	Daily consumption (kg/person)	Daily intake residues (mg/person)
Fat	0.1	1	0.05	0.005
Liver	1.4	1	0.1	0.140
Kidney	10	1	0.05	0.500
Muscle	0.08	1	0.3	0.024
Percentage of ADI (using the JECFA diet)				18.6%

The highest neomycin MRL for mammalian tissues, which are all for cattle tissues except for liver, which is for sheep, has been used in the EDI calculation as a worst case.

Table 16 above demonstrates that the 'estimated daily intake' associated with the proposed MRLs for neomycin is acceptable. For estimations on the chronic dietary exposure associated with the supported uses, Australian consumption data will also be considered using the NEDI calculation.

Chronic Dietary Exposure Assessment

The chronic dietary exposure to neomycin is estimated by the National Estimated Daily Intake (NEDI) calculation, encompassing all registered/temporary uses of the chemical and the mean daily dietary consumption data derived primarily from the FSANZ 2017 Food Consumption Datapack. The 2017 Datapack contains food consumption data from the latest national nutrition survey (2011–12 National Nutrition and Physical Activity Survey). The NEDI calculation is made in accordance with WHO Guidelines and is a conservative estimate of dietary exposure to chemical residues in food. The NEDI for neomycin reflecting overall changes to MRLs, at the end of the phase-out period for non-supported label uses of neomycin, is equivalent to <1% of the ADI of 0.06 mg/kg/bw day. It is concluded that the chronic dietary exposure to neomycin is acceptable.

Acute dietary exposure

The acute dietary exposure for neomycin is estimated by the National Estimated Short Term Intake (NESTI) calculation. The NESTI calculations are made in accordance with the deterministic method used by the JMPR with 97.5th percentile food consumption data derived primarily from the 2011–12 National Nutritional

[6] Food and Agriculture Organization of the United Nations and World Health Organization (FAO), 2011. *Environmental Health Criteria 240 – Principles and Methods for the Risk Assessment of Chemicals in Food*.

and Physical Activity Survey. NESTI calculations are conservative estimates of short-term exposure (24-hour period) to chemical residues in food.

An ARfD has not been established by the APVMA or JECFA for neomycin and a NESTI calculation could therefore not be performed.

Residues and Trade recommendations

Uses supported from a residues and trade perspective

The use of registered product number 37241 is supported for use in cattle sheep, pigs and horses from a residues and trade perspective, however the WHPs, restraints and trade advice statement should be amended as follows:

WITHHOLDING PERIODS:

MEAT: DO NOT USE less than 42 days for cattle, 35 days for sheep and 100 days for pigs before slaughter for human consumption.

MILK: DO NOT USE in lactating or pregnant cows or ewes where milk may be used or processed for human consumption.

RESTRAINTS:

DO NOT USE in horses that may be used for human consumption.

RE-TREATMENT INTERVAL:

DO NOT RE-TREAT cattle for 12 months after the last dose in one course of treatment.

DO NOT RE-TREAT sheep for 4 months after the last dose in one course of treatment.

DO NOT RE-TREAT pigs for 10 weeks after the last dose in one course of treatment.

TRADE ADVICE STATEMENT:

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 57 days for cattle, 56 days for sheep and 100 days for pigs before slaughter for export. Before using this product, confirm the current ESI from the manufacturer on 1800 033461 or the APVMA website (apvma.gov.au/residues).

The use of neomycin on horses currently approved for products 36026, 36237, 37241, 46414 and 49788 is supported from a residues perspective, provided the restraint ‘DO NOT USE in horses that may be used for human consumption’ is added and the current meat WHP for horses be removed from product labels.

Uses NOT supported from a residues and trade perspective

The following uses of neomycin are not supported based on insufficient relevant residues data. Use of:

- feed additive powder product (67805) in poultry, pigs and cattle

- oral solution in water product (52782) in poultry
- intramammary suspension products (49851, 38696) in lactating cows
- certain injectable products (36237) in cattle, sheep and pigs
- oral suspension product (36026,49788) in calves
- oral tablets products (46414) in calves.

Proposed Amendments to the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

Table 17 and Table 18 include the recommended MRL changes in the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023 which will be required as an outcome of the review of registered products. No residues data on the use of neomycin in goats has been submitted and there are currently no registered or permit uses on goats. It is therefore recommended that the currently established MRLs that include goats be deleted from the current Table 1 of the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023.

Table 17: Amendments to Table 1 of the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

Code		Commodity	MRL (mg/kg)	
			Delete	Add
PE	0112	Eggs	T0.5	
MO	0098	Kidney of cattle, goats, pigs and sheep	T10	
MO	0099	Liver of cattle, goats, pigs and sheep	T0.5	
MF	0100	Mammalian fats {except Milk fat}	T0.5	
MM	0095	Meat (mammalian)	T0.5	
ML	0106	Milks	T1.5	
		Poultry, kidney	T10	
		Poultry, liver	T0.5	
PM	0110	Poultry meat	T0.5	
MF	0812	Cattle fat		*0.1
		Cattle muscle		*0.8
MO	1280	Cattle, kidney		10
MO	1281	Cattle, liver		1.3

Code		Commodity	MRL (mg/kg)	
			Delete	Add
		Pig fat/skin		*0.1
		Pig muscle		*0.08
MO	1284	Pig, kidney		*0.2
MO	1285	Pig, liver		*0.2
MF	0822	Sheep fat		*0.1
MO	1288	Sheep, kidney		2.4
MO	1289	Sheep, liver		1.4
		Sheep muscle		*0.08

Table 18: Amendments to Table 3 of the Agricultural and Veterinary Chemicals (MRL Standard for Residues of Chemical Products) Instrument 2023

Compound	Residue	
	Delete	Add
Neomycin	Inhibitory substance, identified as neomycin	Neomycin

Environmental safety

While no specific environmental concerns have been identified resulting from the use of neomycin, consideration of the existing environmental protection and disposal statements on the relevant labels is appropriate.

Recommendations

Environmental protection statement

For large containers (i.e., >1 kg or >1 L), the following statement is required:

> Do not contaminate wetlands or water courses with this product or used containers.

Disposal statements

Disposal statements for small containers and packaging (i.e. up to 1 kg or 1 L), the following statement is required:

> Dispose of container by wrapping with paper and putting in garbage.

Disposal statements for injectable products

In addition to the disposal statements for small containers, the following statement is required where a disposal sharp is distributed with a product or is expected to be used with a product, and sales of the product are not restricted to veterinarians.

> Discarded needles/sharps should immediately be placed in a designated and appropriately labelled ‘sharps’ container.

Disposal statements for feed additives in large containers

The following statements are required for feed additive products, depending on the packaging material (i.e., >1 kg).

> **Paper or cardboard containers and paper material bags**: Shake container into medicated feed. Do not dispose of undiluted chemicals on-site. Break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.
>
> **Plastic bags:** Single-rinse or shake container into the medicated feed. Do not dispose of undiluted chemicals on-site. Puncture bag and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

Metal drums and plastic containers: Triple-rinse container into the medicated feed. Do not dispose of undiluted chemicals on-site. If recycling, replace cap and return clean container to recycler or designated collection point. If not recycling, break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

Disposal statements for oral solutions in large containers

The following statements are required for oral solution products which are supplied in large containers (i.e. >1 L).

Triple-rinse container and dispose of rinsate in compliance with relevant local, state or territory government regulations. Do not dispose of undiluted chemicals on-site. If recycling, replace cap and return clean container to recycler or designated collection point. If not recycling, break, crush, or puncture container and deliver to an approved waste management facility. If an approved waste management facility is not available, dispose of in compliance with relevant local, state or territory government regulations. Do not burn empty containers or product.

Target animal safety

The APVMA published its consideration of target animal safety for product containing neomycin in January 2017 – *Neomycin: Target animal safety risk assessment report*. The assessment concluded that the use of neomycin products registered at that time were generally safe to use in individual animals without renal impairment at recommended doses and routes of administration. No new products containing neomycin which would fall within the scope of this reconsideration have been registered since the publication of this report.

The assessment considered information available to the APVMA including a literature review of information available in the public domain, as well as adverse experience reports (AERs) provided to the APVMA and animal safety studies provided by registrants.

The most frequently reported adverse experience report (AER) was for injection site reactions in horses. The frequency of both Australian and global AERs was low and many appeared to be related to reactions to the procaine benzylpenicillin in one of the neomycin-containing parenteral products.

The information considered indicates that, when administered in high concentrations, for prolonged durations, and/or more than once daily, neomycin may cause nephrotoxicity and/or ototoxicity. This is particularly the case for parenteral formulations. However, the risk of developing nephrotoxicity or ototoxicity from either parenteral or oral formulations increases if the animal has compromised renal function, gastrointestinal inflammation or is receiving another potentially nephrotoxic drug concomitantly.

A close examination of the information considered for food-producing animals suggests that parenteral neomycin-containing products are generally safe to use in healthy target species at recommended dose rates and routes of administration provided they are not administered more than once per day, while oral products are safe to use provided the duration of treatment is restricted, and intramammary products are safe to use in the target species at the recommended dose rate and duration.

As a prescription animal remedy, products containing neomycin can only be prescribed by a veterinarian and used under veterinary supervision. However, additional label warnings in relation to the application of neomycin products are recommended. This includes warnings about the possibility of nephrotoxicity and ototoxicity in food-producing animals and contraindications for the use of neomycin-containing products in animals with compromised renal function, gastrointestinal inflammation or those receiving other potentially nephrotoxic drugs. For parenteral products, the maximum duration of treatment should be clearly indicated, and recommended dosage regimens should be based on extended-interval administration that allows for concentration-dependent killing and avoids extended periods of trough concentrations that lead to accumulation of neomycin. For oral products, the potential for adverse effects following prolonged treatment and clear instructions to re-establish diagnosis if no clinical improvement is seen following the recommended duration of treatment should be included on product labels.

Evidence of local irritation resulting from use of intramammary products was noted.

Conclusions and recommendations

Consideration of the published and unpublished information concerning neomycin use in food-producing animals indicates that neomycin-containing products are generally safe to use in animals without renal impairment at the recommended doses and routes of administration. Information considered under this reconsideration and global and Australian AERs show a low incidence of problems encountered in food-producing animals, when used according to the label directions.

While it is appreciated that the global and Australian incidence of adverse experiences related to the use of neomycin-containing products is low, it is apparent that administration of neomycin at high doses and/or for prolonged duration can be associated with nephrotoxicity and ototoxicity. These should be noted as possible adverse reactions on product labels and the recommended maximum duration of treatment should be clearly indicated.

The risk of nephrotoxicity following parenteral administration of neomycin-containing products decreases when extended-interval (once daily) administration is employed. This information is critical from a toxicity perspective and should be clearly outlined on product labels. The package inserts for parenteral products should elaborate on the importance of once-daily dosing that achieves concentration-dependent killing and sub-toxic trough concentrations, as well as the post-antibiotic effects association with treatment with neomycin.

The risk of developing nephrotoxicity and/or ototoxicity is increased in animals with compromised renal function, gastrointestinal inflammation and those being treated with other potentially nephrotoxic drugs. These situations should be listed as contraindications on product labels.

Label recommendations

The directions for use should indicate a dosage regimen of 24-hour dose interval for parenteral products.

The following contraindications is recommended for all products:

> Not to be used in animals with compromised renal function, gastrointestinal inflammation and those being treated with other potentially nephrotoxic drugs.

The following precaution statement is recommended for all parenteral products:

> Neomycin exhibits concentration-dependent killing and a post-antibiotic effect. Repeated daily administration or overdosage with neomycin can cause renal damage and deafness. Care should be taken in animals with known or suspected impaired renal function. Care should be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs. Where practical, it is recommended to weigh young animals to ensure accurate dosage calculation based on bodyweight.

The risk of nephrotoxicity following oral administration of neomycin-containing products increases when the duration of treatment is prolonged. This information is critical from a toxicity perspective and should be clearly outlined on product labels. The package inserts for parenteral products should elaborate on the

importance of re-establishing the diagnosis if no improvement is observed following the recommended duration of treatment.

The following precaution statement is recommended for all oral products:

> Neomycin exhibits concentration dependent killing and a post-antibiotic effect. Overdosage with neomycin can cause renal damage and deafness. Care should be taken in animals with known or suspected impaired renal function. While this is unlikely at therapeutic doses, care should be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs. Where practical, it is recommended to weigh young animals to ensure accurate dosage calculation based on bodyweight.

For all products that recommend a minimum duration of treatment of 5 days for salmonellosis the following direction should be included:

> If no improvement is seen after 5 days, the diagnosis should be reestablished.

For all intra-mammary products the following precaution statement is recommended:

> Neomycin exhibits concentration-dependent killing and a post-antibiotic effect. Overdosage with neomycin can cause renal damage and deafness. While this is unlikely at therapeutic doses, care should be taken in animals with known or suspected impaired renal function. Care should also be taken in animals being treated with other potentially nephrotoxic substances, such as NSAIDs.

Based on evidence for local irritation following intra-mammary infusion of neomycin for the treatment of mastitis in dairy cattle, the following precaution statement would also be recommended for all intra-mammary products: product labelling.

> If abnormal milk, redness, irritation or swelling persists or increases, discontinue use and redetermine diagnosis.

It is also recommended to remove the use on horses, cattle, sheep and pigs from the label of injectable products where the administration interval specified on the label is less than ‘once daily’ administration (i.e 24 hours).

Efficacy

Each product has previously been assessed as meeting the efficacy criteria if used according to the approved label directions. Based on the review of the information available for neomycin oral, intramammary and injectable products, the APVMA supports the continued use of oral and intramammary products from an efficacy perspective.

The recommendations of the assessment of target animal safety for injectable products, advise that dosage should be limited to once daily administration to reduce the potential for nephrotoxicity and ototoxicity in target animals (i.e. once every 24 hours). As this retreatment interval is outside the current label directions, the APVMA has not previously considered whether we can be satisfied on efficacy of once daily administration. Therefore, use patterns of injectable neomycin chemical products with an administration interval of less than 24 hours (i.e. every 8 to 12 hours) are not supported, noting that a change in the administration interval could affect whether the use of the product would meet the criteria laid out in the Agricultural and Veterinary Chemicals Code (Efficacy Criteria) Determination 2014.

Antimicrobial resistance

Antimicrobial resistance (AMR) occurs when an organism develops resistance to an antimicrobial that is being used to treat it. AMR can develop wherever antibiotics are used, and the level of use increases the likelihood of resistance developing. This is a global public health, animal health and welfare concern. The development and spread of AMR are influenced by both human and animal antimicrobial use.

Global perspective

Globally several studies have reported variable degrees of AMR in neomycin (Yang *et al*. 2021, Wongtawan *et al*. 2022, Ripon *et al*. 2023, El-Adawy *et al*. 2023). Neomycin is listed as critically important for human use in the World Health Organisation's (WHO) list of Critically Important Antimicrobials for Human Medicine (WHO 2019). The WHO recommends the use of this list to help formulate and prioritise risk assessment and risk management strategies for AMR. Neomycin is also on the list of Veterinary Critically Important Antimicrobial Agents (VCIA) as per the World Organisation for Animal Health's (WOAH, founded as OIE) list of antimicrobial agents of veterinary importance (OIE 2021). The inclusion of neomycin in these lists demonstrates that neomycin is an antimicrobial of global importance for both human and veterinary use and should be included in antimicrobial susceptibility programmes. However, the WHO also recognises nation specific considerations should be taken into account, and that this list may vary from country to country (WHO 2019).

Australian situation

The Australian Strategic and Technical Advisory Group on Antimicrobial Resistance (ASTAG) maintains a list of Antibacterial Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia. This list provides information to regulators and users of antibacterials on their importance in the treatment of infections in animals and humans, and the seriousness of the consequences should resistance emerge or be amplified. In this list, neomycin is categorised as an antibiotic with a low importance rating for human and animal health in Australia (ASTAG 2018). A low importance rating signifies that there are a reasonable number of alternative antibacterials in different classes available to treat or prevent most human infections even if antibiotic resistance develops.

In classifying neomycin with a low importance rating for Australia, ASTAG has considered the WHO list of Critically Important Antimicrobials for Human Medicine and the WOAH List of Antimicrobial Agents of Veterinary Importance, along with the local context, Australian surveillance data and available alternative antibiotics. It is specified that the list of Antibacterial Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia has precedence over all other lists, including the WHO's list, to ensure the Australian context is taken into account while determining the requirement for AMR assessment (ASTAG 2018).

Further, to ensure the availability of evidence-based, best practice and nationally consistent approaches to Antimicrobial Stewardship (AMS) across human health and animal health sectors, the Australian Veterinary Association (AVA), under Australia's Antimicrobial Resistance Strategy – 2020 and Beyond, also provides advice on the veterinary use of antibiotics critical to human health. Neomycin is categorised for first line use in animals by the AVA (AVA 2017), where veterinarians are advised to consider using first line antimicrobials

along with alternative treatment approaches following a diagnosis. Antimicrobials categorised for second line use should be limited to where first line antibiotics have been shown to be ineffective, and third line antimicrobials are reserved for last resort use where no other options are available.

For veterinary medicinal use, neomycin is only approved in Australia for the treatment of bacterial infections and as an antimicrobial for use in semen extenders and vaccines. The use of antibiotics as growth promotant (at sub-therapeutic levels) has raised the most concern about selection pressure for AMR. To combat this issue, as per the recommendations from Joint Expert Technical Advisory Committee on Antimicrobial Resistance (JETACAR), no APVMA registered neomycin products include claims for growth promotion, weight gain or feed efficiency. Further, in Australia, all neomycin products are listed as Schedule 4 'prescription only medicine' substances in the Poisons Standard, which limits availability of these products to cases which have been evaluated by a qualified veterinarian. Moreover, neomycin is not registered in Australia for parenteral use in human medicine.

While it is noted that a few recent Australian studies have reported AMR in neomycin (Sahibzada *et al*. 2020, Demiaud and Tee 2022), veterinary antimicrobial products containing neomycin are considered to have a 'low importance' rating for human and animal health in Australia with regards to the development of AMR. The APVMA acknowledges that AMR is a serious concern for all antibiotic products. Considering that there is no reported increase in transfer of neomycin resistant strains among bacteria of major importance in both animals and humans in Australia and no increased reports of cross-resistance with other antimicrobials, the APVMA made a decision not to broaden the scope of the review. APVMA acknowledges that AMR exists for neomycin and to delay its progression, APVMA recommends inclusion of AMR specific label statements.

Recommendations

It is recommended that the following directions/statements should be included in the label instructions for neomycin products used orally, intravenously or intramammary to help reduce the likelihood of AMR developing, as outlined in the APVMA Veterinary Labelling Code.

Under Statement of Claims

> Indiscriminate use of [name of the product] may contribute to the development of antibiotic resistance.

Under General Directions

> Prudent Use: Veterinarian must assess the clinical need for antimicrobials prior to prescription and must communicate the risk of antimicrobial resistance in humans and the need for prudent use in animals. Culture and sensitivity tests may be performed when appropriate to determine susceptibility of the causative organism(s). Empirical therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

It is recommended that the following directions/statements should be included in the label instructions for neomycin products used as a feed additive or additive for animal drinking water to help reduce the likelihood of AMR developing, as outlined in the APVMA Veterinary Labelling Code.

Under Dosage and Administration for feed additive products

Make sure that the animal/s being treated consume all the medicated feed.

Under Dosage and Administration for products used as an additive to animal drinking water

Make sure that the animal/s being treated consume all the medicated water.

Limits have been placed on the ‘off-label’ prescribing of veterinary medicines by Australian Veterinary Association (AVA prescribing guidelines, 2023), Department of Agriculture, Fisheries and Forestry (COAG Reforms, 201022) and APVMA (Veterinary Labelling Code, 2022), by providing guidance to comply with all regulatory label restraint statements. Furthermore, Department of Agriculture, Fisheries and Forestry (Buller *et al*., 2014) and Australian Veterinary Association (AVA prescribing guidelines, 2023) have posed restrictions on the off-label use of Neomycin in food producing animals in Australia. Therefore, the following RESTRAINTS are recommended for neomycin products to prevent their overuse or off-label use.

DO NOT prescribe [Name of Product], prior to investigating the use of non-antibiotic options. If [Name of Product] is indicated and selected for use, prudent prescribing practices (appropriate dose, duration and frequency) should be followed to minimise treatment failure while limiting the possible emergence of antimicrobial resistance.

Appendix

Appendix A – Summary of proposed changes

Product number	Formulation type	Uses supported	Uses not supported	Reason that uses are not supported	Proposed label amendments for uses supported as an outcome of reconsideration
37241	2A – parenteral liquid/solution/suspension	Cattle, sheep, pigs, horses, dogs, cats	N/A	N/A	Amend signal heading, constituent statement withholding periods and disposal instructions. Add additional statement of claims, restraint statement, contraindications, precautions, dosage and administration directions, general directions, trade advice statement, safety directions and storage instructions.
36237	2A – parenteral liquid/solution/suspension	Dogs, cats	Horses, cattle, sheep, pigs	Insufficient residues data for cattle, sheep and pigs. Insufficient efficacy data for horses with required re-treatment interval.	Remove uses on cattle, horses, sheep and pigs and associated withholding periods and trade advice statement. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions and storage instructions.
36026	3A – oral solution/suspension	Horses, dogs, cats	Calves	Insufficient residues data for calves.	Remove use on calves and associated withholding periods and trade advice statement. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions, environmental protection statement and storage instructions.
49788	3A – oral solution/suspension	Horses, dogs, cats	Calves	Insufficient residues data for calves.	Remove use on calves and associated withholding periods and trade advice statement. Amend signal heading, constituent statement and disposal instructions.

Product number	Formulation type	Uses supported	Uses not supported	Reason that uses are not supported	Proposed label amendments for uses supported as an outcome of reconsideration
					Add additional statement of claims, restraint statements, contraindications, precautions, dosage and administration directions, general directions, safety directions, environmental protection statement and storage instructions.
46414	3D – oral tablet	Horses	Calves	Insufficient residues data for calves.	Remove use on calves and associated withholding periods and trade advice statement. Amend signal heading, constituent statement and disposal instructions. Add additional statement of claims, restraint statements. Contraindications, dosage and administration directions, general directions, safety directions and storage instructions.
67805	3H – oral powder, pre-mix	N/A	Poultry, pigs, cattle	Insufficient residues data for poultry, pigs and cattle.	N/A – no supported uses
52782	3H – oral powder, pre-mix	N/A	Poultry	Insufficient residues data for poultry.	N/A – no supported uses
49851	4E – misc. intra mammary	N/A	Lactating cows	Insufficient residues data for lactating cows.	N/A – no supported uses
38696	4E – misc. intra mammary	N/A	Lactating cows	Insufficient residues data for lactating cows.	N/A – no supported uses

Acronyms and abbreviations

Shortened term	Full term
ADI	Acceptable daily intake (for humans)
AER	Adverse experience report
AMR	Antimicrobial resistance
ARfD	Acute reference dose
ASTAG	Australian Strategic and Technical Advisory Group
BP	British Pharmacopeia
Bw	Bodyweight
EDI	Estimated daily intake
ESI	Export slaughter interval
FAO	Food and Agriculture Organization of the United Nations
G	Gram
Kg	Kilogram
L	Litre
Mg	Milligram
MIC	Minimum inhibitory concentration
mL	Millilitre
MRL	Maximum residue limit
NEDI	National estimated Daily Intake
NESTI	National Estimated Short-Term Intake
NOAEL	No Observed Adverse Effect Level
PAE	Post-antibiotic effect
USP	US Pharmacopeia
WHP	Withholding period

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