



# REVIEW SCOPE

Australian Pesticides & Veterinary Medicines Authority

The Reconsideration of Registrations of Products Containing Neomycin (Oral, Intramammary and Injectable Preparations) and Their Associated Approved Labels

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The Australian Pesticides & Veterinary Medicines Authority publishes this review report for oral, intramammary and injectable products, which contain neomycin and their associated approved labels. For further information about this review or the Chemical Review Program, contact:

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## SUMMARY

The APVMA has commenced a reconsideration (hereafter referred to as review), of the registrations of products, which are oral, intramammary and injectable preparations of neomycin and their approved associated labels. This document defines the scope of the review.

The aminoglycoside antibiotic neomycin is contained in a variety of veterinary preparations including topical creams/ointments, eye drops/ointments, oral tablets, oral suspensions, injectables, and intramammary preparations for use in food-producing and non food-producing animals. Two major uses of neomycin are for control of scours in calves and for treatment of mastitis in dairy cattle.

The APVMA will review the following aspects of oral, intramammary and injectable products, which contain neomycin and their associated approved labels:

- a) Residues:
  - i) the potential for residues to exceed standards, and thus pose an undue hazard to the safety of people using anything containing their residues:  
and
  - ii) the adequacy of withholding periods for the use of neomycin in food-producing species.
- b) Trade:
  - i) the potential for residues in export commodities to exceed the tolerances of importing countries, and unduly prejudice trade or commerce between Australia and places outside Australia.
- c) Animal Safety:
  - i) the potential for products which contain neomycin to result in ototoxicity and nephrotoxicity in target food-producing animals.

The review will also consider whether labels for products containing neomycin include adequate instructions and warning statements.

A decision on the review will be made after the APVMA has assessed all the submitted data and other information.

The public is invited to make submissions to the APVMA regarding any of the matters raised in the scope document (see Section 8).

## 1 INTRODUCTION

Section 31 of the Agvet Codes provides that the APVMA may reconsider (review):

- (a) the approval of an active constituent for a proposed or existing chemical product;
- (b) the registration of a chemical product; and
- (c) the approval of a label for containers for a chemical product.

The APVMA has commenced a review of the registrations of products containing neomycin which are oral, intramammary and injectable preparations and their associated approved labels, based on concerns about residues, trade and animal safety.

The aminoglycoside antibiotic neomycin is contained in a variety of veterinary preparations including topical creams/ointments, eye drops/ointments, oral tablets, oral suspensions, injectables, and intramammary preparations for use in food-producing and non-food-producing animals.

The principal concerns raised by State Departments of Primary Industry in the nomination of neomycin for review, relate to (1) residue violations in food-producing animals treated with products, which are oral, intramammary and injectable preparations of neomycin, and (2) animal safety.

No residue or animal safety concerns have been identified for topical formulations, neomycin used as an antibiotic preservation in small animal vaccines and semen extender powder preparations. Therefore, the review of neomycin will only consider products used to treat food-producing animals including oral, intramammary and injectable preparations.

## 2 THE USE OF NEOMYCIN IN AUSTRALIA

### 2.1 Regulatory status

Neomycin is a prescription animal remedy in Schedule 4 (S4) of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). This means that products containing neomycin may only be prescribed by a veterinarian and used under veterinary supervision.

### 2.2 Neomycin products included in the scope of review

At the commencement of the review, there were eight oral (Appendix 1 Table A), three intramammary (Appendix 1 Table B) and three injectable (Appendix 1 Table C) products containing neomycin as the active constituent alone or in combination with another antibiotic. These product registrations are included in the scope of the review. It should be noted that any product registrations that occur after the commencement of the review will also be subject to the outcomes of the review.

## **2.3 Current use patterns of neomycin products included in the review**

Products containing neomycin include a number of different preparations that are used in both food and non-food-producing animals. In food-producing animals neomycin is used to treat intestinal and respiratory infections in cattle and horses and for treatment of mastitis (bacterial infection of the udder caused by microorganisms) in dairy cattle. Oral preparations are used to treat enteric infections in calves. Cattle and horses are treated for respiratory tract infections by intramuscular injection and for mastitis in lactating and non-lactating dairy cows by intramammary infusion.

Other uses for products which contain neomycin in food-producing animals include the oral treatment of pigs which have coliform diarrhoea, oral treatment of chickens and turkeys which have salmonellosis and enteritis, and intramuscular injections in sheep and pigs to treat urinary infections, pasteurellosis, mastitis, metritis and enteric infections.

Products, which are oral and injectable preparations of neomycin, also contain approved label claims for the treatment of bacterial diarrhoea (scours) and infections in dogs and cats.

## **3 REASONS FOR THE REVIEW**

The APVMA has commenced a review of registrations of products containing neomycin which are oral, intramammary and injectable preparations and their associated approved labels in order to determine whether it can be satisfied that continued use of or any other dealing with the products in accordance with the approved instructions for use:

- would not be an undue hazard to the safety of people exposed to them during their handling or people using anything containing their residues; and/or
- would not unduly prejudice trade or commerce between Australia and other places outside Australia; and/or
- would not be likely to have an unintended effect that is harmful to animals, plants, things or the environment.

It also appears that the labels for products containing neomycin may not comply with the prescribed requirements under paragraph 14(3)(d) and contain adequate instructions relating to the matters referred to in paragraph 14(3)(g) of the Agvet Codes.

Therefore, the APVMA decided that product registrations and label approvals for oral, intramammary and injectable preparations of neomycin should be reconsidered under Part 2, Division 4, of the Agvet Codes.

### **3.1 Residue and trade concerns**

State Departments of Primary Industry and the APVMA Chemistry and Residues Program have raised concerns regarding the occurrence of residue violations of neomycin as a result of the use of products containing neomycin, which are oral, intramammary and injectable preparations. The key areas of concern for residue violations of the Australian Maximum Residue Limits (MRLs) are:

- (1) at injection sites and in the kidneys of food-producing animals treated with products which are injectable preparations,
- (2) in the kidneys of food-producing animals treated with products which are oral and intramammary preparations; and
- (3) in the kidneys of young non-ruminating calves after treated with products which are oral formulations.

State Departments of Primary Industry and the National Residue Survey (NRS) have reported that the use of neomycin in food-producing animals has resulted in residues accumulating in the kidneys and at injection sites of treated animals. The Australian Acceptable Daily Intake (ADI) is 0.06 mg/kg/day, based on the ADI set by the Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) in 1996. In early 2004, based on continuing residue violations recorded in Australia, the APVMA set temporary (T) MRLs (listed below) for neomycin in line with revised MRLs established by FAO/WHO Food Standards Codex Alimentarius (Codex). Codex is an international standard setting organisation that formulates and harmonises food standards.

**Table 1: Maximum residue limits of neomycin in food commodities**

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

### 3.2 Animal Safety concerns

Neomycin is one of the aminoglycoside group of antibiotics. Other members of this group include streptomycin, kanamycin and gentamycin.

The aminoglycoside group of antibiotics is well-described in the veterinary literature as having the potential to cause nephrotoxicity (kidney toxicity) and ototoxicity (deafness and/or vestibular symptoms such as unsteadiness) in treated animals.

The APVMA will consider whether oral, intramammary and injectable formulations of neomycin would not be likely to have an unintended effect that is harmful to target food-producing animals.

## 4 SCOPE OF THE REVIEW

The APVMA will review the following aspects of oral, intramammary and injectable products, which contain neomycin and their approved associated labels used in food-producing animals:

- a) Residues:
  - i) the potential for residues to exceed standards, and thus pose an undue hazard to the safety of people using anything containing their residues; and
  - ii) the adequacy of withholding periods for the use of neomycin in food-producing species.
- b) Trade:
  - i) the potential for residues in export commodities to exceed the tolerances of importing countries, and unduly prejudice trade or commerce between Australia and places outside Australia.
- c) Animal Safety:
  - i) the potential for products which contain neomycin to result in ototoxicity and nephrotoxicity in target food-producing animals.

The APVMA will also consider whether product labels (Appendix 1, Tables A – C) carry adequate instructions and warning statements. Such instructions include:

- the circumstances in which the product should be used;
- how the product should be used;
- the times when the product should be used;
- the frequency of the use of the product;
- the re-treatment interval for the product;
- the withholding period after the use of the product;
- the disposal of the product and its container;
- the safe handling of the product and first aid in the event of an accident caused by handling the product;
- any other matter prescribed by the regulations.

## 5 INTERNATIONAL REGULATORY STATUS OF NEOMYCIN

### 5.1 Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)

Neomycin has been considered at the 43<sup>rd</sup>, 47<sup>th</sup>, 52<sup>nd</sup>, 58<sup>th</sup> and 60<sup>th</sup> meetings of JECFA:

- *43<sup>rd</sup> JECFA (1994)*: An ADI based on antimicrobial activity was calculated to be 160 µg/kg bw. However, JECFA considered it was most appropriate to base the ADI on the toxicological data, and set a temporary ADI of 0-30 µg/kg bw, based on a No Observable Effect Level (NOEL) of 6 mg/kg bw/day for ototoxicity in a 90-day study in guinea pigs and a safety factor of 2 x 100 (the extra 2-fold factor to allow for deficiencies in the genotoxicity data).
- *47<sup>th</sup> JECFA (1996)*: Further genotoxicity studies completed since 43<sup>rd</sup> JECFA had become available, were evaluated and judged to be acceptable. As a result, an ADI

of 0-60 µg/kg bw was set, based on the same study as the earlier temporary ADI, but reducing the safety factor to 100.

- *52<sup>nd</sup> JECFA (2000)*: JECFA considered two new residue depletion studies. One study compared tissue residues following oral and intra-muscular administration of neomycin to calves; the second study assessed tissue residue depletion after intramuscular administration of neomycin to cattle. The JECFA concluded that although the MRLs for liver and kidney for cattle established at the 47th meeting were appropriate for oral formulations, the MRLs did not accommodate the use of injectable formulations of neomycin. Accordingly, MRLs for liver and kidney were increased to 500 µg/kg and 10,000 µg/kg, respectively, and MRLs of 500 µg/kg for muscle and fat, and 1,500 µg/L for milk were confirmed for cattle. JECFA also confirmed the MRLs of 10,000 µg/kg for kidney and 500 µg/kg for muscle, fat and liver for chickens, ducks, goats, pigs, sheep, and turkeys, and 500 µg/kg for hen eggs.
- *CCRVDF (13<sup>th</sup> Session, December 2001, Alinorm 03/31)*: It was noted that new toxicological data had become available since the ADI was established and that a re-evaluation of neomycin was required. Neomycin (toxicity) was added to the Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation. The United States agreed to provide the toxicological data to JECFA.
- *58<sup>th</sup> JECFA (2002)*. Information was considered on the registration of injectable neomycin products. Consideration was also given to a CCRVDF report on target animal safety.
- *60<sup>th</sup> JECFA (February 2003)*: The ADI was maintained at 0-60 µg/kg bw on the basis of assessment of new toxicological data flagged in 2001.

## 5.2 International use of neomycin

In the USA, Canada and South Africa, injectable neomycin products are not authorised for use in food animals. This is based on a high risk of target animal toxicity. Neomycin is registered for use in Europe and the UK.

## 6 DATA ASSESSMENT AND POSSIBLE OUTCOMES

The APVMA will conduct a technical assessment of data submitted for the review of neomycin.

The review can result in one of three broad outcomes:

- The APVMA remains satisfied that products containing neomycin continue to meet the conditions to which registration or approval are currently subject, and affirms the registrations and approvals; or
- The APVMA is satisfied that the conditions to which the registration or approval is currently subject can be varied in such a way that the requirements for continued registration or approval will be complied with, and varies the conditions of approval or registration; or

- The APVMA is not satisfied that the conditions to which the registration or approval is currently subject continue to be met and suspends or cancels the registration or approvals.

The data might lead the APVMA to revise or establish MRLs.

The APVMA will have regard to appropriate public health standards including the ADI in its review of product registrations.

## **7 CONSULTATION THROUGHOUT THE REVIEW PROCESS**

From initiation of the review through to the implementation of the review outcomes, the APVMA will consult with relevant stakeholders and interested parties.

The APVMA will publish a Preliminary Review Findings (PRF) report, including the review findings and proposed regulatory decision. A period will be allowed for the stakeholders and the public to comment on the PRF.

## **8 SUBMISSIONS FROM THE PUBLIC ARE INVITED**

Interested groups or individuals are invited to make a submission or provide data relevant to the concerns raised in this scope document. Submissions must reach the APVMA by no later than **11 May 2007**. Submissions can be sent either by email to [chemrev@apvma.gov.au](mailto:chemrev@apvma.gov.au) or by mail to:

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**Appendix 1: Neomycin products to be included in the review****Table A: Oral preparations**

Product number	Product Name	Registrant	Label approval number
36026	Scourban Oral Anti-diarrhoeal Suspension	Bomac Laboratories Limited (NZ)	36026/1201 36026/01
41468	Bronson and Jacobs Pty Ltd Neomycin Sulphate AG Grade	Bronson and Jacobs Pty Limited	Ψ
46414	VR Neo-Sulcin Scour Tablets	Jurox Pty Limited	46414/0101
49788	Scour-X Oral Anti-diarrhoeal Suspension	Jurox Pty Limited	49788/0101 49788/01
52621	Neomycin Sulphate Upjohn Feed Additive Powder	Pfizer Animal Health a Div of Pfizer Australia Pty Ltd	52621/0802 52621/0100
52782	CCD Neomycin (Neomycin Sulphate Water Soluble Powder)	Ridley Agriproducts Pty Ltd T/A CCD Animal Health	52782/2/0705 52782/1003 52782/1100
54091	AAH Neomycin Sulphate Feed Additive Powder	Goodwale Pty Ltd T/A Allied Animal Health	54091/0802 54091/0901
58671	Neopharm Antibiotic Feed Additive	Bomac Animal Health Pty Limited	58671/500g/0205 58671/1kg/0205 58671/10kg/0205

Ψ Labels transitioned from the States and not having an approval number

**Table B: Intramammary preparations**

Product number	Product Name	Registrant	Label approval number
38696	Special Formula 17900 Forte-V Lactating Intramammary Antibiotic Suspension	Pfizer Animal Health a Div of Pfizer Australia Pty Ltd	38696/0402 38696/0899
38698	Lincocin Forte Lactating Intramammary Antibiotic Solution	Pfizer Animal Health a Div of Pfizer Australia Pty Ltd	38698/0402 38698/0899
49851	Mastalone Blue Intramammary Suspension for Lactating cows	Pfizer Animal Health a Div of Pfizer Australia Pty Ltd	49851/01

**Table C: Injectable preparations**

Product number	Product Name	Registrant	Label approval number
36237	Jurox Neomycin Sulphate Injection	Jurox Pty Limited	36237/100mL/0305 36237/02
36693	Neoject 200 Antibiotic Injection	Delvet Pty Ltd	Ψ
37241	Neomycin Penicillin 100/200 Aqueous Suspension for Intramuscular Injection	Intervet Australia Pty Limited	37241/100M/1006 37241/100M/0405 37241/250M/0405 37241/100M/0504 37241/250M/0504 37241/0301

Ψ Labels transitioned from the States and not having an approval number