Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Active Monepantel in the Product Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for assessing and approving agricultural and veterinary chemical products prior to their sale and use in Australia.

In undertaking this task, the APVMA works in close cooperation with advisory agencies, including the Department of Health and Aging, Office of Chemical Safety and Environmental Health (OCSEH), Department of the Environment, Water, Heritage and the Arts (DEWHA), and State Departments of Primary Industry.

The APVMA has a policy of encouraging openness and transparency in its activities and of seeking community involvement in decision making. Part of that process is the publication of public release summaries for all products containing new active ingredients.

The information and technical data required by the APVMA to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the APVMA's publication *Vet MORAG: Manual of Requirements and Guidelines*.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the APVMA and its 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.

About this document

This is a Public Release Summary.

It indicates that the Australian Pesticides and Veterinary Medicines Authority (APVMA) is considering an application for registration of an agricultural or veterinary chemical. It provides a summary of the APVMA's assessment.

Comment is sought from industry groups and stakeholders on the information contained within this document.

Making a submission

In accordance with sections 12 and 13 of the Agvet Code, the APVMA invites any person to submit a relevant written submission as to whether the application for registration of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep should be granted. Submissions should relate only to matters that the APVMA is required by legislation to take into account in deciding whether to grant the application. These grounds include **occupational health and safety, chemistry and manufacture, residues, safety and first aid, environmental fate and toxicity, trade** and **efficacy**. Submissions should state the grounds on which they are based. Comments received outside these grounds cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **Monday 5 July 2010** and be directed to the contact listed below. All submissions to the APVMA will be acknowledged in writing via email or by post.

Relevant comments will be taken into account by the APVMA in deciding whether the product should be registered and in determining appropriate conditions of registration and product labelling.

When making a submission please include:

- Contact name
- Company or Group name (if relevant)
- Postal Address
- Email Address (if available)
- The date you made the submission.

All personal and ***confidential commercial information (CCI)***[1] material contained in submissions will be treated confidentially.

Written submissions on the APVMA's proposal to grant the application for registration that relate to the **grounds for registration** should be addressed in writing to:

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Further information

Further information can be obtained via the contact details provided above.

Further information on public release summaries can be found on the APVMA website: http://www.apvma.gov.au

[1] A full definition of "confidential commercial information" is contained in the Agvet Code.

1 INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Novartis Animal Health Australasia Pty Ltd for registration of a new product, Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep, containing the new active constituent monepantel. This publication provides a summary of the data assessed and an outline of the regulatory considerations for the proposed registration of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

Internal parasites are a major problem in sheep in Australia. Anthelmintics are used to control worms in sheep, however development of resistance to the commonly used anthelmintics is becoming an increasing problem.

Monepantel is a new amino-acetonitrile derivative (AAD) anthelmintic with a novel mode of action. It acts on a nematode-specific ACR-23 nicotinic acetylcholine receptor sub-unit.

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is an oral drench that contains 25 mg/mL monepantel.

The proposed use is for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

The proposed dose rate is 2.5 mg monepantel/kg bodyweight (1 mL Zolvix/10 kg bodyweight). Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is administered as a single treatment. If repeat treatments are necessary, sheep are not to be retreated less than 21 days after the last treatment and after 3 consecutive treatments, 115 days must elapse before treating again with Zolvix.

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep will be packaged in 0.25L, 0.5L, 1L, 2.5L, 5L and 10L containers.

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is currently registered in New Zealand, Uruguay and 27 countries in the European Union.

The APVMA seeks public comment on the product outlined in this document prior to the product being registered for use in Australia. The APVMA will consider all responses received during the public consultation period in deciding whether the product should be registered and in determining conditions of registration and product labelling.

2 CHEMISTRY AND MANUFACTURE

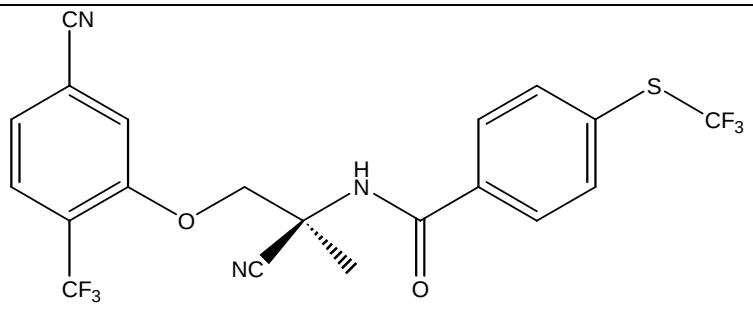
2.1 ACTIVE CONSTITUENT

Monepantel is a new active constituent and there is no compendial specification available.

The Pharmaceutical Chemistry Section of the APVMA has evaluated the chemistry aspects of monepantel (manufacturing process, quality control procedures, batch analysis results and analytical methods).

The chemical active constituent monepantel has the following properties:

COMMON NAME (ISO):	Monepantel (INN)
CHEMICAL NAME:	*N*-[(1*S*)-1-Cyano-2-(5-cyano-2-fluoromethylphenoxy)-1-methylethyl]-4-trifluoromethylsulfanylbenzamide
CHIRALITY:	The active substance has one chiral centre and possesses two enantiomers: the active (*S*)-enantiomer and the inactive (*R*)-enantiomer, which is considered an impurity
PRODUCT NAME:	Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep
CAS REGISTRY NUMBER:	887148-69-8
EMPIRICAL FORMULA:	$C_{20}H_{13}F_6N_3O_2S$
MOLECULAR WEIGHT:	473.39
PHYSICAL FORM:	Powder
COLOUR:	White
OPTICAL ROTATION:	-32° ($[\alpha]_{580\ nm}$)
MELTING POINT:	142-149 °C (form B), 125 °C (form A)
DENSITY:	1.468 g/cm^3
OCTANOL/PHOSPHATE BUFFER (PH 7) PARTITION COEFFICIENT (LOG POW):	4.2-4.7 (@ 20 °C)
POLYMORPHISM (FORM B):	Orthorhombic
VAPOUR PRESSURE AT 25^{O}C:	2.8 x 10^{-11} hPa (extrapolated value)
SOLUBILITY	Practically insoluble in water (0.08 mg/L), slightly soluble in propylene glycol (6.9 g/L) and n-octanol (7.3 g/L), soluble in ethanol (60.7 g/L) and freely soluble in polyethylene glycol 300 (156.1 g/L) and dichloromethane (175 g/L)

STRUCTURAL FORMULA:	

2.2 PRODUCT

Dose form: Oral drench

Formulation type: Non-aqueous solution

Level of active: 25 mg/mL monepantel

Physical properties – Appearance: clear yellow to orange solution

Storage and stability

The applicant provided the results of real time and accelerated stability testing conducted using samples stored in the proposed commercial containers. The results indicate that the formulated product is expected to be stable for the duration of the shelf life when stored below 30 °C (room temperature) in the proposed commercial packaging. After initial opening, the product is expected to be stable for 12 months when stored below 30 °C (room temperature) in the proposed commercial packaging.

Packaging

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep will be packaged in 0.25, 0.5, 1, 2.5, 5 and 10 L fluorinated HDPE bottles or laminated aluminium pouches. The integrity of the container materials was demonstrated in the storage stability studies. The product is not expected to have an adverse effect on the packaging and the packaging is not expected to have an adverse effect on the product.

2.3 RECOMMENDATION

The Pharmaceutical Chemistry Section of the APVMA has evaluated the chemistry and manufacturing aspects of the monepantel and is satisfied that all the data requirements (including the physico-chemical properties, spectral identification, manufacturing and quality control aspects, impurity formation, active constituent specification, stability, batch analysis data, analytical methods and packaging information) necessary for the approval of this new active constituent have been met.

The Pharmaceutical Chemistry Section of the APVMA has evaluated the chemistry and manufacturing aspects of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep and is satisfied that all the data requirements (including the formulation composition, manufacturing and quality control aspects, product specification, batch analysis, stability, analytical methods, packaging and label) necessary for the approval of this new veterinary chemical product have been met.

The Pharmaceutical Chemistry Section of the APVMA is satisfied that the chemistry requirements of Sections 14(4) and 14(5) Agricultural and Veterinary Chemicals Codes have been met.

3 TOXICOLOGICAL ASSESSMENT

3.1 EVALUATION OF TOXICOLOGY

The Office of Chemical Safety and Environmental Health (OCSEH) within the Department of Health and Ageing, Australia has conducted the toxicology assessment of monepantel.

The toxicological database for monepantel is quite extensive and consists primarily of toxicity tests conducted in laboratory animals. In interpreting the data it should be noted that toxicity tests generally use doses that are high compared with likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified.

Findings of adverse effects in any one species do not necessarily indicate such effects might be generated in humans. However, from a conservative risk assessment perspective, adverse findings in animal species are assumed to represent potential effects in humans unless convincing evidence of species specificity is available. Where possible, considerations of the species-specific mechanisms of adverse reactions weigh heavily in the extrapolation of animal data to likely human hazard. Equally, consideration of the risks to human health must take into account the likely human exposure levels compared with those, usually many times higher, which produce effects in animal studies.

Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes (ADI and ARfD) at which no adverse health effects in humans would be expected.

Toxicokinetics and Metabolism

Monepantel was only moderately absorbed in rats (up to approximately 50%) after oral administration. Excretion was mainly via the faeces, with no unchanged monepantel following intravenous administration. After oral administration, between 52% and 75% monepantel was found unchanged in the faeces. No unchanged compound was found in the urine of either oral or intravenous treated animals. Tissue distribution was poor and was restricted to hair follicle, liver, subcutis, white fat, skin and the salivary gland.

Elimination of radiolabelled monepantel occurred almost exclusively by biotransformation, mono exponentially with a terminal half-life between 40 and 60 hours. The metabolites in plasma were comparable following intravenous and oral administration. The main metabolite, M2, was attributed to the sulfone derivative of the parent compound. Additionally, up to seven minor or trace metabolites were detected in plasma extracts. Similar metabolites were observed after multiple dosing. Bile did not contain any parent compound. A glucuronide (M6) was the main metabolite in bile, which was easily hydrolysed by ß-glucuronidase, yielding M3.

When radiolabelled [^{14}C] monepantel was formulated as a 2.5% solution and applied topically to rats, the estimated dermal absorption of monepantel was approximately 6%.

Acute toxicity studies

Acute toxicity studies demonstrated that monepantel has low acute oral and dermal toxicity in rats (LD_{50}s both > 2000 mg/kg bw). The compound was not a skin irritant but a slight eye irritant in rabbits. It was not a skin sensitiser in mice. No information is available on the acute inhalational toxicity of monepantel.

The formulated product, Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep, has low acute oral and dermal toxicity in rats (LD_{50}s both > 2000 mg/kg bw). It was a slight skin and eye irritant in rabbits and a skin sensitiser in mice. No information is available on the acute inhalational toxicity of the formulated product.

Short term and subchronic toxicity studies

Wistar rats (5/sex/dose) were administered monepantel [0, 1000, 4000, 12000 ppm] in the diet *ad libitum* for 4 weeks. Clinical signs were limited to superficial skin lesions in one high dose female rat. The liver was identified as the primary target organ. Clinical biochemistry effects included decreased glucose levels and increased lipid parameters (triglycerides, phospholipids and cholesterol) in medium and high dose males and in all monepantel treatment groups in females. Liver weight changes were observed at all doses in female rats and in the medium and high dose males. Centrilobular hypertrophy lesions were observed in the liver in both sexes at all test item doses. Diffuse follicular hypertrophy lesions were also observed in the thyroid gland in males at all test item doses and in medium and high dose females. The severity and incidence of the lesions were dose dependent. No NOEL could be established due to effects observed at all doses.

Beagle dogs (2/sex/dose) were administered monepantel [0, 5000, 15000, 40000 ppm] for four weeks. Decreased food consumption and body weight loss were observed at the high dose in males. Increased alkaline phosphatase levels were observed at all monepantel dose levels in both sexes, although without a dose response relationship. Dose-related decreases were observed in the absolute and relative thymus weights in all treated animals of both sexes. Higher adrenal gland weights were recorded in all treated animals of both sexes. Increased liver weights were observed in females at 5000 and 15000 ppm and increased thyroid gland and liver weights were recorded in a single female at the 40,000 ppm treatment level. Microscopic investigation showed minimal to moderate thymus involution in all high dose treated animals. A NOEL for this 4-week dog study could not be established due to effects including elevated alkaline phosphatase levels and reduced thymus weights, which were seen at the lowest monepantel dose level.

SD rats were given monepantel daily in the diet for 90 days at concentrations of 0, 50, 200, 1000 and 12000 ppm. Reduced prothrombin time (PT) was observed at monepantel doses of 1000 ppm and above in both sexes. Reduced partial thromboplastin time (PTT) and neutrophil count and increased absolute platelet count were observed in females at the high dose level. Urine pH and the concentrations of Na^+, Cl^-, cholesterol and phospholipids in the blood of female rats were all affected at doses of 1000 ppm and above. A significant reduction in aspartate aminotransferase (ASAT) levels was observed in female rats at 200 ppm and 12000 ppm monepantel and the liver of female animals was mostly affected at 1000 ppm and above. At 12000 ppm there were pathologies of the ovary in 3/10 rats. Effects on testes consisted of hypospermatogenesis in 8/10 males dosed at 12000 ppm. Blood albumin and Na^+ concentrations were also affected when monepantel was given to male rats at 1000 ppm and above. There was a significant reduction in the bilirubin level at doses of 1000 ppm and above. In the 12000 ppm group, this reduction in bilirubin

concentration was not reversed even 4 weeks after monepantel was withdrawn. Overall, the NOEL is 200 ppm (14 mg/kg bw/d)

In a 13-week dietary study, male and female beagle dogs were fed monepantel at 0, 300, 3000 or 30000 ppm daily for 90 days. Most treatment-related changes were observed in groups dosed at 3000 ppm monepantel and above. In the blood, there was reduced activated partial prothrombin time concomitant with a mild but significant reduction in Ca^{2+} level at 3000 ppm and above in males and 30000 ppm in females. At the highest dose, both sexes had increased albumin concentration and albumin/globulin ratio. Male dogs given 3000 ppm or above had increased total plasma protein concentrations. Alkaline phosphatase (ALP) was markedly increased in both sexes at 3000 ppm and above. Organs mostly affected by monepantel administration were the liver, small intestine and pancreas. There were dilated glands of the duodenum and jejunum in both sexes of dogs as well as an increase in the liver weight of female dogs at 300 ppm and above. These monepantel-related effects were mostly reversible within 4 weeks of the test item being withdrawn from the diet. No NOEL could be established given the treatment-related effects in liver and small intestine seen at the lowest dose studied.

CD-1 mice of both sexes were dosed with monepantel in the diet *ad libitum* at concentrations of 0, 30, 120, 600 or 6000 ppm for 13 weeks. The liver was the target organ of toxicity. A dose-related increase in total bilirubin was observed at the two highest doses in males and in females. Cholesterol concentrations were increased in a dose-related manner in both sexes. An increase in the incidence and severity of hepatic focal necrosis was seen in females at 600 ppm and above. Treatment-related focal necrosis of the liver was also seen in males at 6000 ppm. A NOEL of 120 ppm (17.97 mg/kg bw/d) has been established for this study, based on hepatic focal necrosis (females only at 600 ppm), fatty changes in the liver, and elevated lipid parameters in both sexes at 600 ppm and above.

Long term toxicity and carcinogenicity studies

In a 52-week chronic oral toxicity study, Wistar rats were dosed with monepantel in the diet *ad libitum* at concentrations of 0, 50, 200, 1000 or 12000 ppm. Monepantel-related changes included increased lipid, protein, albumin and globulin levels and decreased glucose levels in the blood at 12000 ppm. Dose related increases in the absolute liver weight, the liver to body weight ratio and liver to brain weight ratios were observed at 1000 ppm and above. The NOEL based on the results of this study for monepantel administered orally via the diet is 200 ppm (10.67 mg/kg bw).

Beagle dogs were administered monepantel at dietary concentrations of 0, 100, 300 and 3000 ppm for 52 weeks. Treatment-related effects consisted of a decrease in activated partial thromboplastin time in males and females at 300 ppm and above, an increase in fibrinogen levels in males and an increase in alkaline phosphatase activity as well as thyroid weight in males and females. Other changes at 300 ppm and above included changes in liver weight in females (with histopathological changes), an increase in the incidence and severity of intestinal gland dilation in males and females as well as an increased incidence in brown pigments in tubular cells of the kidney in males. Therefore, overall, the lowest dose of 100 ppm (equivalent to 2.96 mg/kg bw/d) was established as the NOEL for this study.

In a 78-week oncogenicity study, monepantel was administered *ad libitum* to CD-1 mice at dietary concentrations of 0, 10, 30, 120 and 500 ppm. Mortality rate was slightly increased in females dosed at 500 ppm compared to the control (34% vs 14%). Increases were observed in liver weights at 120 ppm and above

and spleen weights at 500 ppm, together with findings of fatty liver changes at 120 ppm and above. Monepantel treatment did not reveal a carcinogenic potential. The NOEL for this study is 30 ppm (4.2 mg/kg bw/d).

In a 104-week oncogenicity (feeding) study, Wistar rats were given monepantel at dietary concentrations of 0, 100, 1000 and 12000 ppm. Reduced body weight was observed at 12000 ppm and increases in the liver, kidney and heart weights, albeit without microscopic findings, were observed at 1000 ppm and above. Based on the results of this study, monepantel is not carcinogenic in rats. The NOEL for this study is 100 ppm (4.63 mg/kg bw/d).

Reproduction and Developmental Studies

In a 2-generation reproduction study, rats received 0, 200, 1500 or 12000 ppm of monepantel in the daily diet prior to pairing, throughout pairing, gestation and lactation for two generations. In the absence of any reproductive effects up to and including the top dose of 12000 ppm, the NOEL for reproductive toxicity in this 2-generation study is 12000 ppm (647 mg/kg bw/d). For systemic toxicity, a NOEL of 200 ppm (10.5 mg/kg bw/d) was established based on increased absolute and relative liver weights in conjunction with hepatocellular hypertrophy, and increases in cortical cell hypertrophy of the adrenal glands at 1500 ppm and above in P and P1 generation females.

In a developmental study, female rats cohabited with males until copulation was confirmed. The assumed pregnant rats then received 0, 100, 300 or 1000 mg/kg bw/day of monepantel by gavage from day 6 to day 20 of pregnancy. There were no treatment-related effects in this study. The NOEL in this study for both maternal and developmental toxicity was 1000 mg/kg bw/day, the highest dose tested. Given that monepantel exhibited systemic toxicity in other repeat dose studies (i.e. liver toxicity at doses lower than 1000 mg/kg bw/d) and some relevant parameters (organ weights and histopathology, haematology and clinical chemistry) were not measured in this study, it is considered that the maternal NOEL value observed in this study has limited value and the true maternal NOEL value could be below 1000 mg/kg bw/d.

In a second developmental study, female rabbits cohabited with males until copulation was confirmed. The assumed pregnant rabbits received 0, 100, 300 or 1000 mg/kg bw/d of monepantel by gavage from day 6 to day 27 of pregnancy. Food consumption was sometimes lower than controls in all treated groups without a dose-relationship but body weight gains were not affected. There were limited findings at 1000 mg/kg bw/d of an undescribed palate abnormality in a single animal in 2 litters and an observation of the aorta being duplicated from the bladder to kidneys and unstructured tissue within the nasopharynx in foetuses from a single litter. These were not considered to provide sufficient evidence that monepantel is hazardous for developmental toxicity. However, the NOEL for developmental toxicity was 300 mg/kg bw/day based on the above limited findings, while the NOEL for maternal toxicity was 1000 mg/kg bw/d as no maternal toxicity was observed in this study.

Genotoxicity Studies

No evidence of a mutagenic potential for monepantel was observed in a battery of *in vitro* and *in vivo* genotoxicity assays that assessed gene mutation and/or chromosome aberration.

Neurotoxicity Studies

No neurotoxicity tests were available for evaluation.

3.2 PUBLIC HEALTH STANDARDS

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under State poisons regulations to prevent the occurrence of poisoning.

The available data indicate that monepantel is of low acute toxicity, is a slight eye irritant, would pose a relatively low hazard from repeated use and is unlikely to produce irreversible toxicity. The NDPSC agreed that the low acute oral and dermal toxicity, with only slight eye irritation and dermal irritation potential constituted a risk that could be adequately addressed through a Schedule 5 listing. The Committee decided to include a new entry in Schedule 5 for monepantel.

NOEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is that quantity of an agricultural or veterinary chemical compound that can safely be consumed on a daily basis for a lifetime and is based on the lowest NOEL obtained in the most sensitive species. This NOEL is then divided by a safety factor, which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

The ADI for monepantel was established at 0.03 mg/kg bw/day, based on a NOEL of 100 ppm (2.96 mg/kg bw/day) in a 52-week dietary study in beagle dogs and applying a safety factor of 100.

The acute reference dose (ARfD) is the maximum quantity of an agricultural or veterinary chemical that can safely be consumed as a single, isolated event. The ARfD is derived from the lowest NOAEL (NOEL) as a single or short-term dose that causes no effect in the most sensitive species of experimental animal tested, together with a safety factor that reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals.

An ARfD for monepantel has not been established and there are insufficient data to enable an ARfD to be set.

4 RESIDUES ASSESSMENT

4.1 INTRODUCTION

Monepantel is a new anthelmintic, currently not registered for use in any animal species in Australia. Therefore, Maximum Residue Limits (MRLs) for monepantel in edible sheep tissues need to be established to cover the proposed product use-pattern. These MRLs have been set using the JECFA MRL-setting approach (as adopted by the APVMA on 1 July 2006).

4.2 DATA PROVIDED

The Applicant provided details of metabolism studies that were conducted with monepantel in a range of animal species, including rats, dogs and sheep. Additionally, details of three tissue residues decline trials conducted in sheep with the proposed formulation were provided.

4.3 EVALUATION SUMMARY

Metabolism of monepantel

Absorption

Monepantel is well absorbed following oral administration. In rats, following a single oral administration of 10 mg [^{14}C] monepantel/kg bw, peak mean plasma concentrations of ^{14}C (1.26 ± 0.61 µmol/L) were reached 2 hours after treatment, and declined constantly until 96 hours after the treatment, with only trace amounts remaining in blood and plasma (0.004 µmo/L). When sheep were administered a single oral dose of 1.66 mg or 4.60 mg [^{14}C] monepantel/kg, peak blood concentrations of monepantel and monepantel sulphone (M2) were reached at 8 and 24 hours, respectively, after treatment.

Distribution

In rats, following daily administration of [^{14}C] monepantel for 7 days, 6 hours after the last treatment, highest tissue residues were found in liver (0.6-2.0 %) and fatty tissue (0.3-2.9 %), followed by adrenal gland, pancreas and ovaries. The other organs sampled contributed <0.1 % to the total radioactivity.

When sheep were administered a single oral dose of 5 mg [^{14}C] monepantel/kg bw it was found that highest mean total radioactivity residue (TRR) concentrations occurred in fat (19.3 mg equivalents/kg bw) at 2 days after treatment (the first sampling time). Highest mean TRR concentrations in liver (66.7 mg equivalents/kg bw) were observed at 2 days after treatment also. Radioactivity in all edible tissues showed a steady decline and the rank order for total radioactivity in edible tissues was fat>liver>>>muscle>kidney.

Metabolism

The metabolism of monepantel involves: (i) oxidation of monepantel to monepantel sulphoxide (M1), followed by a rapid oxidation to monepantel sulphone (M2) and a slower oxidation to M3; (ii) cleavage to

produce M4 and its sulphate conjugate (M5); and (iii) hydrolysis to produce an alcohol and an acid, which are eliminated via the urine.

When sheep were administered a single oral dose of 5 mg [^{14}C] monepantel/kg bw, monepantel sulphone was the main metabolite. Monepantel was a minor constituent and was found only at the earlier sampling times. The decline of monepantel sulphone residues is mirrored by the decline of TRRs in all edible tissues. Therefore, monepantel sulphone is an appropriate marker residue for liver, kidney, muscle and fat.

Excretion

Monepantel is excreted mainly in the faeces. When sheep were administered a single oral dose of 5 mg [^{14}C] monepantel/kg bw, 14 days after treatment, total radioactivity recovered and accounted for was 94-98 %. The radioactivity was excreted mainly through the faeces and bile (53-61 %), and urine (~30 %).

In faeces, the main metabolite was monepantel sulphone, followed by monepantel, especially at the early sampling times. Urinary metabolites identified were M4 (phenol) and M5 (sulphate).

Comparative metabolism

The pharmacokinetic profiles of the veterinary chemical and its metabolites in the target animal species must be qualitatively comparable with those of the laboratory animal species used to establish the health standards, to verify the relevance of the toxicological effects and NO(A)ELs, and thereby validate the dietary exposure assessments. Based on the available metabolism data, it is concluded that the metabolism of monepantel in sheep is qualitatively similar to that determined in laboratory species (dogs and rats).

Summary

Monepantel sulphone was the main metabolite in edible tissues. Monepantel and monepantel sulphone accounted for most of the TRRs in edible tissues, with other minor metabolites identified having no toxicological significance. The decline of monepantel sulphone residues is mirrored by the decline of TRRs in all edible tissues. Therefore, monepantel sulphone is an appropriate marker residue for liver, kidney, muscle and fat. The relative rank order for monepantel residues in edible tissues is: fat>liver>>>muscle>kidney.

Analytical method

Details were provided for a validated analytical method that could be used to determine monepantel residues in edible tissues from sheep. The method involves monepantel sulphone being extracted from homogenised tissue samples with acetonitrile, cleaned up on SPE cartridges, and analysed using an HPLC method coupled with UV detection. The concentration of monepantel sulphone is determined using a standard calibration curve of peak response to external standard concentration.

The Limits of Quantification (LOQs) and Limits of Detection (LODs) for the analytical method are tabulated below.

Table 1: The Limits of Quantification (LOQs) and Limits of Detection (LODs) for the analytical method

TISSUE MATRIX	LOQ (µg/kg)	LOD (µg/kg)
Liver	10	3.6
Muscle	10	4.5
Kidney	10	4.7
Fat	10	6.3

Residue definition

Monepantel sulphone is an appropriate marker residue for monepantel, as the sulphone metabolite represents a large and relatively constant fraction of total residues in all edible tissues. Therefore, the residue definition for monepantel is '*monepantel sulphone'*.

The ratio of marker residue to total residues is 0.94 for muscle, and 0.68 for fat, liver and kidney.

Residues Trials

Three tissue residues trials were conducted with Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep. In each trial, sheep (n=32-48) were administered a single oral drench of 3.75 mg monepantel/kg bw (ie 1× maximum label dose rate). Groups of animals (n=8) were sacrificed at specified times ranging from 7 to 127 days after treatment. Samples of liver, kidney, muscle, subcutaneous fat and peri-renal fat were collected and analysed for their concentrations of monepantel residues. The residues results from these three trials are combined and presented graphically below.

Monepantel sulphone (AHC 2144670) residues in all edible tissues from sheep that were administered a single oral treatment at the maximum proposed label rate

Figure 1: AHC 2144670 residues in peri-renal fat from sheep administered a single oral dose of 3.75 mg AHC 2102225/kg bw (1× maximum dose rate)

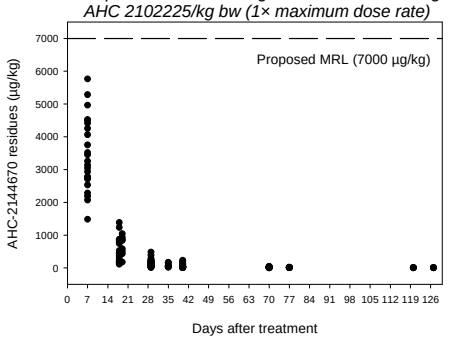


Figure 2: AHC 2144670 residues in subcutaneous fat from sheep administered a single oral dose of 3.75 mg AHC 2102225/kg bw (1× maximum dose rate)

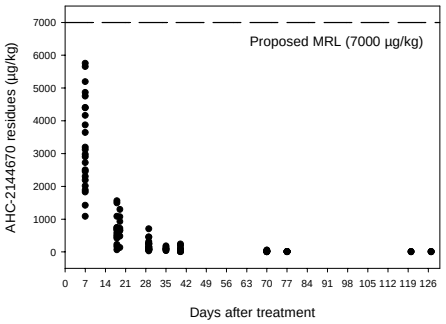


Figure 3: AHC 2144670 residues in muscle from sheep administered a single oral dose of 3.75 mg AHC 2102225/kg bw (1× maximum dose rate)

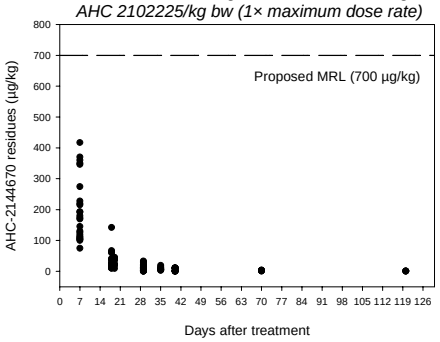


Figure 4: AHC 2144670 residues in kidney from sheep administered a single oral dose of 3.75 mg AHC 2102225/kg bw (1× maximum dose rate)

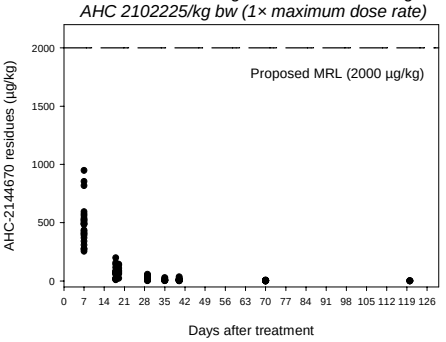
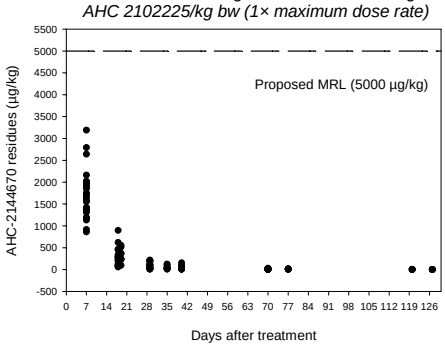


Figure 5: AHC 2144670 residues in liver from sheep administered a single oral dose of 3.75 mg AHC 2102225/kg bw (1× maximum dose rate)



Highest monepantel sulphone residues occured in fat and liver. Consequently, it is the decline of monepantel sulphone residues in sheep fat and liver (the target tissues) that determines the length of the domestic withholding period (WHP), the re-treatment interval, and the Export Slaughter Interval (ESI) for the use of the new product in sheep.

MRL recommendations

The following monepantel MRLs are recommended to cover the occurrence of monepantel residues in edible sheep tissues after the 14 day WHP has been observed: sheep muscle - 0.7 mg/kg; sheep fat - 7 mg/kg; sheep liver - 5 mg/kg; sheep kidney - 2 mg/kg.

Withholding period - Meat

Statistical analysis of the residues data indicates that monepantel residues in all edible sheep tissues will have declined to below the relevant recommended monepantel MRLs at 14 days after treatment. Therefore, a 14 day meat WHP is recommended for the use of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

Withholding period - Milk

In the absence of any milk residues data, the following milk WHP is recommended:

"*DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption*".

Re-treatment interval

The Applicant conducted a residues trial where sheep were administered 3.75 mg monepantel/kg bw (ie 1× maximum label dose rate) at 21 day intervals. Groups of animals were sacrificed at 21 days after the second, third and fourth treatment, as well as 14 days after the fourth treatment. Samples of liver and peri-renal fat were collected and analysed for their concentrations of monepantel residues. Statistical analyses comparing monepantel sulphone residues in peri-renal fat and liver of sheep following a single oral dose and 4 consecutive treatments 21 days apart indicate that there is no significant difference between monepantel sulphone residues in tissues following a single oral dose and 4 consecutive treatments 21 days apart. However, the residues data show a decline in monepantel sulphone residues at 21 days after the 2nd and 3rd treatments, but not after the 4th treatment. Therefore, a minimum re-treatment interval of 21 days is supported, with a maximum of three treatments. After the third treatment, a period of 115 days (i.e. the time taken for monepantel residues to decline to LOQ) must be observed before further treatment.

Fat solubility and potential for bioaccumulation

The report of the Thirty-eighth Session of the Codex Committee on Pesticide Residues (April 2006) revisited the issue of fat-soluble pesticides in meat and fat. The meeting decided to revise the empirical limits recommended by the 1991 JMPR when considering log P_{ow}, so that when no evidence is available to the contrary and log P_{ow} exceeds **3**, the compound would be designated fat-soluble, and when log P_{ow} is less than 3 it would not be so designated.

The octanol/phosphate buffer partition coefficient (log P_{ow}) for monepantel is 4.2-4.7. Accordingly, monepantel is considered fat-soluble. However, it is concluded that the potential for monepantel to bioaccumulate is low, as the results from residues trials demonstrate that residues of monepantel do not accumulate in either fat or liver of treated sheep.

Dietary risk assessment

Chronic dietary exposure assessment

The chronic dietary exposure to monepantel residues 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 from the 1995 National Nutrition Survey of Australia. 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 monepantel is equivalent to 3.14 % of the ADI. It is concluded that the chronic dietary exposure to monepantel is acceptable.

Acute dietary exposure assessment

The acute dietary exposure 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 from the 1995 National Nutrition Survey of Australia. NESTI calculations are conservative estimates of acute exposure (24 hour period) to chemical residues in food. To date, the Office of Chemical Safety and Environmental Health (OCSEH) has not established an Acute Reference Dose (ARfD) for monepantel. Therefore, no estimate of the acute dietary exposure to monepantel has been performed.

4.4 CONCLUSIONS AND RECOMMENDATIONS

Registration of the product

The Veterinary Residues Team (VRT) has evaluated the residues aspects of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep. The VRT has considered the available metabolism, residue trials, analytical methodology, fate in storage, processing data and residues in trade issues, including that submitted by Novartis Animal Health Australasia Pty Limited to support their application to register a new oral product for use in sheep.

The VRT recommends that the APVMA be satisfied that the use of the product in accordance with the required label instructions would not be harmful or an undue hazard to the safety of people exposed to residues in food as per section 14(3)(e)(i) & (ii) and that the residues aspects of section 14(5) of the Agvet Codes have been met.

The VRT supports the following label instructions for Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep:

ANIMAL	PURPOSE	DOSE RATE
Sheep	For the treatment and control of intestinal nematodes.	Nominal: 1 mL product/10 kg bw (i.e. 2.5 mg monepantel/kg bw) Maximal: 1.5 mL product/10 kg lamb (i.e. 3.75 mg monepantel/kg bw)

Restraints:

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Retreatment interval:

DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

Withholding Periods:

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Trade Advice:

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT slaughter for export less than 115 days after treatment.

Recommended amendments to the MRL standard

The following amendments to the *MRL Standard* are recommended:

Table 2: MRL Standard - Table 1 Amendments

Table 1

COMPOUND	FOOD		MRL (mg/kg)
ADD:			
MONEPANTEL	MM 0822	Sheep muscle	0.7
	MF 0822	Sheep fat	7
	MO 1288	Sheep kidney	2
	MO 1289	Sheep liver	5

Table 3: MRL Standard – Table 3 Amendments

Table 3

COMPOUND	RESIDUE
ADD:	
Monepantel	Monepantel sulphone

5 ASSESSMENT OF OVERSEAS TRADE ASPECTS OF RESIDUES IN FOOD

Commodities exported

Australian exports of mutton/lamb and live sheep could be affected by the use of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

Destination of Exports

Consultation within Commonwealth and State Government agencies and with the Sheepmeat Council of Australia has determined that the APVMA will consider the standards of China, Commonwealth of Independent States (CIS), European Union (regarded as 27 countries as of January 2007), Japan, Saudi Arabia, United Arab Emirates (UAE) and USA, along with the Maximum Residue Limit Standard of the Codex Alimentarius Commission, when determining Export Slaughter Intervals.

Overseas registration and approved label instructions

Novartis Animal Health Australasia Pty Ltd has indicated that Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is registered in the European Union, New Zealand and Uruguay.

Comparison of Australian MRLs with Codex and overseas MRLs

The Codex Alimentarius Commission (Codex) is responsible for establishing Codex Maximum Residue Limits for pesticides and veterinary medicines. Codex Maximum Residue Limits are primarily intended to facilitate international trade and accommodate differences in Good Agricultural Practice (GAP) employed by various countries. Some countries may accept Codex Maximum Residue Limits when importing foods. Monepantel has not been considered by Codex and MRLs have only been established in the European Union and New Zealand. Comparisons of the recommended Australian and overseas residues definitions and MRLs/tolerances for monepantel are tabulated below.

Table 4: Comparison of the recommended Australian and overseas monepantel MRLs/tolerances

COMMODITY	OVERSEAS MRLs/TOLERANCE (mg/kg)								RECOMMENDED AUSTRALIAN MRL (mg/kg)
	Codex	European Union	USA	China	Japan	CIS[1]	Saudi Arabia	UAE[2]	
Sheep muscle	--	0.7	--	--	--	--	--	--	0.7
Sheep fat	--	7.0	--	--	--	--	--	--	7.0
Sheep liver	--	5.0	--	--	--	--	--	--	5.0
Sheep kidney	--	2.0	--	--	--	--	--	--	2.0

[1] Commonwealth of Independent States (CIS)

[2] United Arab Emirates (UAE)

Potential risk to trade

Export of treated produce containing finite (measurable) residues of monepantel 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.

Currently, the European Union is the only country amongst those considered by the APVMA when determining ESIs, with monepantel MRLs for sheep muscle, fat, liver and kidney (0.7 mg/kg, 7.0 mg/kg, 5.0 mg/kg and 2.0 mg/kg, respectively) and these MRLs are equivalent to the recommended Australian monepantel MRLs. China, CIS, Japan, Saudi Arabia, UAE, USA and Codex do not have MRLs/tolerances for monepantel in sheep commodities. Therefore, these are considered to be the most sensitive export markets for Australian sheep commodities containing monepantel.

Identification of the appropriate ESI 'endpoint'

In the absence of importing standards for monepantel residues in edible tissues in China, CIS, Japan, Saudi Arabia, UAE, USA and Codex, it is concluded that the appropriate 'endpoint' for determination of the ESI for Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is the LOQ of the validated analytical method (i.e. 0.01 mg/kg).

Estimation of the ESI

Statistical analysis (using the EMA Meat Program) of the residues data indicates that monepantel residues in fat, liver, kidney and muscle from treated sheep are likely to be below 0.01 mg/kg at 115 days after treatment. Therefore, an ESI of 115 days has been recommended for the use of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

Conclusion

Overall, the risk to Australia's export trade in sheep commodities is considered to be low when the recommended ESI of 115 days is observed for Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep.

The Veterinary Residues Team (VRT) recommends that the APVMA be satisfied that the use of the product in accordance with the required instructions would not unduly prejudice trade and commerce between Australia and places outside Australia as per section 14(3)(e)(iv) of the Agvet Codes, as monepantel sulphone residues in edible tissues from sheep are expected to have declined to levels below the standards applied by the importing countries when the recommended ESI of 115 days is observed.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

6.1 HEALTH HAZARDS

Monepantel has low acute oral and dermal toxicity in rats. It is not a skin irritant but a slight eye irritant in rabbits. It was not a skin sensitiser in mice. No information is available on its acute inhalational toxicity. Monepantel is not listed on the Australian Safety and Compensation Council (ASCC) Hazardous Substances Information System (HSIS) Database (ASCC, 2005)

The formulated product, Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep, has low acute oral and dermal toxicity in rats. It was a slight skin and eye irritant in rabbits and a skin sensitiser in mice. No information is available on its acute inhalational toxicity. Based on the product toxicology information and concentrations of monepantel and other ingredients in the product, the product is classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following risk phrases:

R43	May cause sensitisation by skin contact
R38	Irritating to skin

6.2 FORMULATION, PACKAGING, TRANSPORT, STORAGE AND RETAILING

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep will be available as a liquid in high-density polyethylene (HDPE) bottles with induction heat-sealed caps and/or laminated aluminium pouches in the following pack sizes: 250mL, 500mL, 1L, 2.5L, 5L and 10L. Transport workers and store persons who handle the packaged products could only become contaminated if packaging was breached.

6.3 USE PATTERN

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is a new anthelmintic that is active against economically important nematodes in sheep, including strains resistant to other classes of anthelmintics. The product will be available at a concentration of 25 mg monepantel /mL and will be administered undiluted by oral drenching.

6.4 EXPOSURE DURING USE

Farmers and their employees will be the main users of the product. Workers may be exposed to the product when opening containers, administering the product (or connecting containers to a drenching gun, using the drenching gun), and cleaning up spills and equipment. Hand contamination is also possible if the animals cough during administration, when refilling the backpack, if the drenching gun becomes blocked or when cleaning equipment. The potential for exposure during administration of Zolvix Monepantel Broad Spectrum

Oral Anthelmintic for Sheep is largely via the dermal route. A user guide video at the Novartis Zolvix web site: http://www.zolvix.com/optimum/using/shtml provides more information on the drenching procedure.

There was no worker exposure study provided for monepantel or the product. Instead, two approaches to enable an operator exposure assessment were constructed.

These estimations, in conjunction with the toxicology data, showed that for Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep, the use of elbow length chemical resistant gloves is required to protect workers.

6.5 EXPOSURE DURING RE-ENTRY

As the product is administered directly into the animal's mouth, exposure is not expected to occur during re-handing of animals. Therefore, there is no risk associated with re-handling animals treated with this product.

6.6 RECOMMENDATIONS FOR SAFE USE

Users should follow the First Aid Instructions and Safety Directions on the product label.

FIRST AID INSTRUCTIONS

If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

6.7 CONCLUSION

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep can be used safely if handled in accordance with the instructions on the product label and any other control measures described above. Additional information is available in the product MSDS.

OCSEH recommends that the APVMA can be satisfied that the proposed use of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep would not be likely to have an effect that is harmful to human beings when used in accordance with label instructions.

7 ENVIRONMENTAL ASSESSMENT

7.1 INTRODUCTION

Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep contains the new active constituent (ac) monepantel at 25 mg ac/mL and will be administered orally as a drench at a maximum dose of 3.75 mg ac/kg body weight. It is expected that young animals could receive several treatments during their first year of life while older animals will receive only a single annual dose. Environmental exposure is expected to primarily involve excreta in pastures, with aquatic exposure also possible through run-off.

7.2 ENVIRONMENTAL CHEMISTRY AND FATE

Hydrolysis

Based on its chemical structure, monepantel is expected to be stable to hydrolysis under environmental conditions but may hydrolyse under severe conditions.

Photodegradation

Monepantel is not expected to be readily photodegradable based on its UV-visible absorption spectrum.

Biodegradation

Aerobic soil metabolism

An aerobic metabolism of [^{14}C]-monepantel in 3 different soil types treated at a rate of 0.3 mg ac/kg soil indicated that monepantel has half-lives between 38 and 146 days: the lower the fraction of sand in the soil, the faster the degradation of monepantel. At the end of the studies, the total recovery (mass balance) was 75 – 86% of the initial. Most of the applied radioactivity in all 3 soils was extractable. Less than 1% of the total applied radioactivity was measured in the volatile degradation products (including carbon dioxide). The amounts of radioactivity extracted from the soil samples decreased over the test duration while the amounts of non-extractable residues in the soil increased during the course of the experiment.

Metabolism in animals

The pharmacokinetics, metabolism, distribution and excretion of monepantel have been evaluated in rats. Uptake and elimination are rapid and a substantial portion of the parent compound is excreted metabolised. After repeated oral administration for 7 days, the major proportion (60-80%) of the applied radioactivity was recovered in faeces and 3-6% in urine. In the faeces, the parent represented 25% of the mean daily dose and the metabolites **>**52%.

A study was conducted to investigate the absorption, distribution, metabolism and excretory patterns of monepantel in sheep at oral dose rates of 1.7 and 4.6 mg ac/kg bw. The amount of radioactivity recovered was 109-114%. Within 12 days, 87-92% were eliminated. At the time of slaughter, 17-27% remained in the

animal and was found mostly in fat (11-21%) and muscle (4%). Pharmacokinetics in blood as well as residues in faeces and tissue were dominated by the active sulfone metabolite AHC 2144670 and to a much lesser extent the parent compound. In urine, no parent compound or sulfone was detected, whereas two prominent urinary metabolites were discovered: AHC 2166636 and AHC 2166637.

Another study was conducted to investigate the residue depletion as well as absorption, distribution, metabolism and excretion of [^{14}C]-AHC 2102225 (monepantel) after a single oral administration to sheep at a dose rate of 5 mg ac/kg bw. The mean recovery of radioactivity from urine was about 30%, faeces 53-61% and cage wash 1.8-4.2% of the administered dose. Peak mean Total Radioactive Residue (TRR) concentrations in urine and faeces were observed between 24 and 72 h post dose and decreased steadily thereafter. The highest overall mean TRR concentration was observed in urine and faeces at 48 h. Most of the radioactivity was excreted within two weeks, with the faecal pathway being the prominent one. Faecal metabolites were structurally close to the parent compound, whereas urinary metabolites corresponded to the products as a result of the cleavage via the ether linkage of the parent.

Mobility

Soil adsorption/desorption studies

Adsorption/desorption of radiolabelled monepantel was determined in 5 different soil types (sand, two lots of loamy sand with varying amounts of organic content, clayey loam and loam). A quantitative balance of radioactivity was established. The adsorption constants (K_d) in the five test soils ranged from 81 to 295 mL/g and the corresponding adsorption coefficient (K_{oc}) values were 6082 to 8880 mL/g. Based on McCall's Mobility Classifications, monepantel is considered to be immobile in these 5 soils. Desorption of monepantel from the five different soil types was recalculated at up to 20% of the amount adsorbed. The adsorption process is considered not to be reversible.

Bioaccumulation in aquatic organisms

Bioaccumulation studies were not undertaken. Based on the determined value of log K_{ow} 4.2-4.7, it is likely that monepantel has the potential for bioaccumulation in aquatic organisms. However, it is metabolised in sheep and release to the aquatic compartment will be low.

7.3 ENVIRONMENTAL EFFECTS

Aquatic organisms

Monepantel is considered to be non-toxic to aquatic organisms (fish, aquatic invertebrates, algae) up to its limit of water solubility. These were based on Water Accommodated Fraction (WAF) tests at 100 mg WAF/L, with measured values ranging from 0.1-2 mg ac/L.

Non-target Invertebrates (Terrestrial)

Earthworms

The NOEC for mortality, growth, reproduction and feeding activity of the earthworm was 2.4 mg ac/kg dry soil for an exposure period of 56 days.

Dung Flies

The test item had no effect on hatching rate of flies and development time at 1000 mg ac/kg dry dung. The NOEC for development of the fly *Scathophaga stercoraria* from eggs to adults is 1000 mg ac/kg dung, indicative of a non-toxic effect.

Arthropods

No test for toxicity to dung beetle larvae was performed but at concentrations of up to 640 mg ac/L, monepantel had no activity against any of the arthropods such as cat flea, blowfly, chicken red mite, adult dog tick and domestic fly. In addition, the main metabolites of sulfoxide and sulfone found in treated animals were determined to be inactive against these arthropods. Based on the available information monepantel has low activity to a range of arthropods.

Soil Microorganisms

Monepantel did not have an impact on soil microflora, based on the respiratory activity and the soil nitrogen transformation at a concentration of up to 0.3 mg ac/kg dry soil. It is concluded that the active constituent does not have a long-term influence on soil microflora.

Phytotoxicity

Monepantel did not show any effects on seedling emergence and seedling growth for oilseed rape, soybean and oat. The germination rate was not statistically significantly reduced for all species tested. Neither mortality nor phytotoxic effects were observed for all plants species tested. It is concluded that monepantel has no significant adverse effect on germination and growth of non-target plants at a concentration of 100 mg ac/kg dry soil.

7.4 PREDICTION OF ENVIRONMENTAL RISK

Aquatic organisms

DEWHA's environmental risk calculations in the aquatic compartment are based on a worst-case pasture scenario with direct excretion into surface water by grazing sheep and a worst-case run-off in a feedlot situation under Australian farm practices for sheep.

Given the acute toxicity of the aquatic organisms was determined to be non-toxic up to its limit of water solubility of 0.1 mg ac/L and a $PEC_{surface\ water}$ of 0.4 µg/L, the resultant risk quotient indicates an acceptable

environmental risk to the aquatic organisms from direct discharge of a fraction of the excreta into a slow flowing stream under a pasture scenario.

A 5% run-off as a result of rainfall into a pond in a feedlot scenario results in a concentration of 4.2 µg ac/L contained in a pond. The risk quotient calculation indicates an unacceptable environmental risk is unlikely to occur in the aquatic compartment as a result of run-off.

Residual quantities of monepantel are not expected to leach from decaying sheep faeces as a result of rainfall because of the active constituent's low water solubility and its strong association with soil and organic matter. The decay of sheep faeces contaminated with monepantel on grazing land or in a feedlot is therefore not expected to constitute an environmental risk to aquatic invertebrates.

Non-target invertebrates and micro-organisms

The PEC in the terrestrial compartment under Australian farm practices was estimated to be 1.7 and 150 µg ac/kg dry soil in pastures and feedlots, respectively, based on 100% of the excreted drug as parent compound.

The proposed registration of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep under Australian farm practices is not expected to present unacceptable risks to arthropods, dung flies and earthworms, or to have lasting effects on soil respiration and nitrification processes. This is based on studies showing that the calculated PECs are well below the toxicological end points tested, which showed no adverse effects.

Non-target vegetation

Monepantel has no significant adverse effect on germination of non-target plants at a concentration of 100 mg ac/kg dry soil. At the soil concentration of 1.7 µg ac/kg dry soil, it is clear that there is unlikely to be an environmental effect on non-target vegetation in pastures.

7.5 CONCLUSION

Given the low toxicity of monepantel to aquatic organisms and its expected low concentration in water, the environmental risk as a result of discharge to water in a pasture environment and from run-off in a feedlot scenario is considered acceptable.

On the basis of the low concentration of the active constituent present in treated soils based on the proposed use pattern and the low toxicity to arthropods, dung flies, micro-organisms and vegetation, there is unlikely to be an environmental risk to terrestrial organisms in pastures or feedlots.

In order to be satisfied that the proposed uses of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep will not lead to an unintended effect that is harmful to animals, plants or the environment at the proposed rate and following good agricultural practice, DEWHA recommends the following disposal statement for pack sizes greater than 1L (HDPE or aluminium packaging):

"Triple rinse containers before disposal. Dispose of rinsate or any undiluted chemical according to State/Territory legislative requirements. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. DO NOT burn empty containers or product."

For pack sizes 1L or less (HDPE or aluminium packaging), the following disposal statement is recommended:

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

Acceptance of this recommendation allows DEWHA to recommend that the APVMA be satisfied that the proposed use of Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep would not be likely to have an unintended effect that is harmful to animals, plants, or things or to the environment.

8 EFFICACY AND SAFETY ASSESSMENT

Monepantel is a new amino-acetonitrile derivative (AAD) anthelmintic with a novel mode of action. It acts on a nematode-specific ACR-23 nicotinic acetylcholine receptor sub-unit.

The proposed claims are for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including those macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains.

Zolvix will be administered at 2.5 mg monepantel/kg bodyweight (1 mL Zolvix/10 kg bodyweight).

8.1 EVALUATION OF EFFICACY DATA

The efficacy data included a range of parasites in both artificial and natural infection pen studies and field situations. The studies were well monitored and the analysis was compliant with both WAAVP and APVMA guidelines.

The pen studies included:

Fourth Stage Larval (L4) Nematodes:

- Three Dose Determination Studies (including two conducted in Australia)
- Two Formulation Bridging Studies (including one conducted in Australia)
- Nine Dose Confirmation Studies (5 conducted in Australia, 3 in Europe and one in New Zealand)

Adult Stage Nematodes

- Three Dose Determination Studies (including two conducted in Australia)
- One Formulation Bridging Study (conducted in Australia)
- Nine Dose Confirmation Studies (6 in Australia and 3 in Europe).

The field studies included two multi-centre field efficacy studies (one each in Australia and New Zealand).

TYPE OF STUDY	AUSTRALIA		NEW ZEALAND		EUROPE	
	L4	Adult	L4	Adult	L4	Adult
Dose determination	2	2	--	--	1	1
Formulation ‘bridging’	1	1	--	--	--	1
Dose confirmation	5	6	1	--	3	3
Field efficacy	1 (12 sites)		1 (18 sites)		--	

The dose determination studies tested three doses of monepantel at 1.25, 2.5 and 5.0 mg/kg bw against a range of larval and adult stages of nematodes. Untreated animals served as controls. Sheep were artificially infected with third stage larvae prior to treatment. In some trials, sheep were infected with known resistant strains (benzimidazole, levamisole and benzimidazole+levamisole). Total worm counts were conducted 2 weeks (Australia) or 3 weeks (Europe) after treatment. Efficacy against most parasites and stages was generally >95% at 5.0 and 2.5 mg/kg, consequently a dose of 2.5 mg/kg was selected for the dose confirmation studies.

The bridging studies were conducted to demonstrate the continuity of data between the near final and final oral formulations of monepantel. The results indicated that there was no significant difference between the efficacies of the two formulations.

The dose confirmation studies investigated the efficacy of monepantel at 2.5 mg/kg bw against a range of larval and adult stages of nematodes. Untreated animals served as controls. Sheep were artificially or naturally infected with nematodes prior to treatment. In some trials, sheep were infected with known resistant strains (benzimidazole, levamisole and benzimidazole+levamisole). Faecal egg counts were conducted 1-2 weeks after treatment (2 weeks in Australia/New Zealand). Total worm counts were conducted 1.5-3 weeks after treatment (2 weeks in Australia/New Zealand). Efficacy against most parasites and stages was generally >95%.

The field studies investigated the efficacy of monepantel at 2.5 mg/kg bw against natural infections of gastrointestinal nematodes in sheep grazing pasture. In addition to a negative control group, a range of positive control groups was also included, with products representing the macrocyclic lactone, benzimidazole and imidazothiazole classes. Faecal egg counts were conducted 1, 2 and 3 weeks after treatment. Efficacy against the parasite populations was >95%. The parasite populations included macrocyclic lactone, benzimidazole, levamisole and benzimidazole+levamisole resistant strains.

The efficacy studies demonstrated that Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep is effective (>95%) against a range of adult and immature fourth larval stages of gastro-intestinal nematodes of sheep.

Claims for the following nematode species and stages are supported, when the product is used at the proposed label dose rate of 1 mL Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep/10 kg bodyweight:

Haemonchus contortus (adult and immature L4)

Teladorsagia (Ostertagia) circumcincta (adult and immature L4)

Teladorsagia (Ostertagia) trifurcata (adult and immature L4)

Teladorsagia (Ostertagia) davtiani (adult and immature L4)

Trichostrongylus colubriformis (adult and immature L4)

Trichostrongylus vitrinus (adult and immature L4)

Trichostrongylus rugatus (adult and immature L4)

Trichostrongylus axei (adult and immature L4)

Nematodirus filicollis (adult and immature L4)

Nematodirus spathiger (adult)

Cooperia curticei (adult and immature L4)

Cooperia oncophora (adult and immature L4)

Chabertia ovina (adult and immature L4)

Oesophagostomum venulosum (immature L4)

The claims of efficacy against macrocyclic lactone, benzimidazole, levamisole and morantel resistant strains of gastrointestinal nematodes are also supported.

No adverse events due to systemic activity of monepantel were reported in any of the studies.

8.2 EVALUATION OF TARGET ANIMAL SAFETY DATA

The applicant provided a comprehensive set of target animal safety studies. This included:

- Two Preliminary Studies
- Two pivotal studies at 1x, 3x, 5x (repeat dose) and 10x (single dose) maximum label dose
- One repeat dose reproductive safety study at 3x maximum label dose in ewes and rams.

The pivotal and reproductive studies were conducted to Good Laboratory Practice. Except for the first preliminary study, the target animal safety studies were conducted with the final formulation.

In the first preliminary study, adult Suffolk ewes (11 months old) received 50 and 75 mg monepantel/kg bw orally and then two weeks later, another 100 and 125 mg/kg. At 100 mg/kg, only a slightly decreased haemoglobin concentration was apparent. Likely treatment-related changes at 125 mg/kg included a transient decrease of appetite, increases in fluoride oxalate glucose, serum glucose and urea concentrations, increased alanine aminotransferase concentrations and decreased haemoglobin concentrations. The maximum dose tested equated to 33x the maximum label dose of 3.75 mg/kg. Sheep tolerated the single dose levels well, without toxicologically significant changes in the observed parameters.

In a second preliminary study, 2-3 week old Suffolk lambs weighing 9-11 kg were administered a single dose of 2 mL product/kg bw (50 mg monepantel/kg bw; 13x maximum label dose). Untreated lambs served as controls. Immediately after treatment all lambs demonstrated signs of depression. One fatality occurred due to aspiration during treatment. No other gross or histopathological abnormalities were observed. Apart from the single fatality, the dose was clinically well tolerated.

One pivotal study investigated the safety of a single dose of 37.5 mg monepantel/kg bw (10x maximum label dose) in 2-4 week old Merino and Suffolk lambs weighing 7-14 kg. Control animals were dosed with saline. Variable signs of depression were observed in most lambs immediately after treatment. Increased respiratory rates were seen in three lambs treated with monepantel. Three lambs died within 48 h after treatment due to aspiration pneumonia and the pathological evidence supported this conclusion. The pathological assessment indicated that several surviving lambs aspirated small volumes of fluid during treatment. No significant treatment-related macroscopic or microscopic changes were found in the surviving animals. No toxicologically meaningful differences in haematological, coagulation or clinical chemistry variables were found. The lambs grew at normal rates and there were no differences in bodyweight between control and treatment groups. No specific treatment-related adverse effects were identified and no differences in response to treatment were noted between Merino and Suffolk lambs.

The second pivotal study investigated the repeat dose safety of the product in 12-15 week old Merino lambs treated at 1x, 3x and 5x the maximum label dose rate (3.75 mg/kg bw). Control animals were dosed with saline. The study commenced shortly after lambs were weaned. No treatment-related adverse events were reported. There was no difference in feed consumption and water consumption between the treated and control groups. There was no difference between the body weights of treated and control animals at any time point. There were no relevant differences in the organ weight, the organ weight/body weight and the organ weight/brain weight ratios at necropsy in any group. No specific treatment-related adverse effects were identified and no differences in response to treatment were noted. Repeated oral administration of the formulation at 1x, 3x and 5x the maximum label dose was well tolerated in young, growing Merino lambs.

A repeat dose reproductive safety study was conducted at 3x the maximum label dose. The product was administered orally at 11.25 mg monepantel/kg bw at repeated intervals throughout an entire spermatogenic cycle and mating for Merino rams and throughout the follicular phase of reproduction, the gestational period and after parturition until weaning to Merino ewes to identify potential adverse effects on male and female fertility and reproductive performance and on offspring viability. Control animals were dosed with saline. The trial was designed to investigate ram-specific treatment effects, ewe-specific treatment effects and potential combinatory effects of treatment of both sexes. A series of reproductive parameters were assessed and in addition, necropsy and gross pathological examination were conducted on a subset of animals. No significant differences were detected between treated and control animals in reproductive parameters. No significant macroscopic changes were found at necropsy in the treated animals compared to the control animals.

The safety studies demonstrate that the margin of safety is satisfactory to support safe administration at the label dose (of 2.5mg monepantel/kg bw and up to the maximum recommended dose per weight range of 3.75 mg monepantel/kg bw) and frequency in male and female lambs from two weeks of age weighing at least 10 kg and in breeding animals of both sexes. A small number of animal fatalities occurred due to misapplication into the respiratory tract rather than due to toxicity of the test item. The application of a 10-fold volume would have increased this risk, especially in young lambs. There were no reported differences between Merino and Suffolk sheep; both tolerated the treatment equally well. There were no significant differences detected in the reproductive study.

8.3 CONCLUSIONS

The pen and field studies demonstrate that Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep at 1 mL/10 kg bw will be effective for the treatment of control of AAD-sensitive strains of gastro-intestinal nematodes, including macrocyclic lactone, benzimidazole, levamisole and morantel-resistant strains in sheep.

The target animal safety studies and efficacy studies demonstrate that the label dose of monepantel is well tolerated by sheep, including lambs from 2 weeks of age weighing at least 10 kg and breeding ewes and rams.

The APVMA concludes that Zolvix Monepantel Broad Spectrum Oral Anthelmintic for Sheep would not be likely to have an unintended effect that is harmful to sheep and would be effective when used according to label instructions.

9 LABELLING REQUIREMENTS

HDPE packsizes 0.25L, 0.5L and 1L

Bottle – Label front panel

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

0.25L, 0.5L, 1L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

Batch Number:	
Expiry Date:	

Bottle– – Label back panel

READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration
Use remaining product within 12 months of opening the container.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS
May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

APVMA Approval No.
62752/0.25L/mmyy
62752/ 0.5L/mmyy
62752/1L/mmyy

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

BAR CODE
DRUMMUSTER LOGO

Multifolded zipseal leaflet for 0.25L, 0.5L, 1L (HDPE)

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

0.25L, 0.5L, 1L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 0.25L	No. Treated/ 0.5L	No. Treated/ 1L	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	166	333	666	1666	3333	6666
16–20	2.0	125	250	500	1250	2500	5000
21–25	2.5	100	200	400	1000	2000	4000
26–30	3.0	83	166	333	833	1666	3333
31–35	3.5	71	142	285	714	1428	2857
36–40	4.0	62	125	250	625	1250	2500
41–50	5.0	50	100	200	500	1000	2000
51–60	6.0	41	83	166	416	833	1666
61–70	7.0	35	71	142	357	714	1428
71–80	8.0	31	62	125	312	625	1250

Sheep in excess of 80 kg body weight should be dosed at 1 mL/10 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest sheep by liveweight in each group (ewes, wethers, rams, lambs). DO NOT under dose. Where there is a large variation in size within the group, dose rates should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. A correct drenching technique is recommended; carefully place the drench gun nozzle in the side of the mouth and over the back of the tongue before delivering the dose.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

ZOLVIX contains MONEPANTEL, a member of the new Amino-Acetonitrile Derivative class of anthelmintics that has a novel mode of action. It is effective against sensitive strains of the following internal parasites [Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***]** in sheep.

* Includes ***adult and immature L4 stage***

Resistance may develop to any chemical. Ask your local veterinary practitioner or animal health adviser for recommended parasite management practices for your area to reduce development of resistance. It is advisable that a resistance test be conducted before any parasite treatment is used.

SAFETY TO SHEEP

The safety of this product has not been established in lambs less than 2 weeks of age or 10kg bodyweight. ZOLVIX has a wide margin of safety when used as recommended and is readily accepted by sheep. Pregnant and breeding sheep may be treated provided normal care is taken in handling.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, waterways or drains with the product or used containers. Do not discharge waste liquid into streams.

Disposal
The container can be recycled if it is clean, dry, free of visible residues and has the *drumMUSTER* logo visible. Triple or pressure rinse container for disposal. Dispose of rinsate or any undiluted chemical according to State legislative requirements. Wash outside of the container and the cap. Store cleaned container in a sheltered place with cap removed. It will then be acceptable for recycling at any *drumMuster* collection or similar container management program site. The cap should not be replaced but may be taken separately. DO NOT burn empty containers or product.

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

WARRANTY AND EXCLUSION OF LIABILITY
This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations or liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia **8.30 am to 5.30 pm E.S.T. Monday to Friday**

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

DRUMMUSTER LOGO

Carton front panel: 0.25L, 0.5L, 1L

CAUTION
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

0.25L, 0.5L, 1L

PICTOGRAM

NOVARTIS LOGO

Carton back panel: Bottle back label & multifolded leaflet to be affixed on back panel of carton

READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration
Use remaining product within 12 months of opening the container.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS
May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

APVMA Approval No.
62752/0.25L/mmyy
62752/ 0.5L/mmyy
62752/1L/mmyy

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

® Registered trademark of Novartis AG, Basel, Switzerland.

BAR CODE
DRUMMUSTER LOGO

HDPE packsizes 2.5L, 5L and 10L

HDPE – Label front panel

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

2.5L, 5L, 10L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

Batch Number:	
Expiry Date:	

HDPE– Label back panel

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	1666	3333	6666
16–20	2.0	1250	2500	5000
21–25	2.5	1000	2000	4000
26–30	3.0	833	1666	3333
31–35	3.5	714	1428	2857
36–40	4.0	625	1250	2500
41–50	5.0	500	1000	2000
51–60	6.0	416	833	1666
61–70	7.0	357	714	1428
71–80	8.0	312	625	1250

Sheep in excess of 80 kg body weight should be dosed at 1 mL/10 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest sheep by liveweight in each group (ewes, wethers, rams, lambs). DO NOT under dose. Where there is a large variation in size within the group, dose rates should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. A correct drenching technique is recommended; carefully place the drench gun nozzle in the side of the mouth and over the back of the tongue before delivering the dose.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

ZOLVIX contains MONEPANTEL, a member of the new Amino-Acetonitrile Derivative class of anthelmintics that has a novel mode of action. It is effective against sensitive strains of the following internal parasites [Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***]** in sheep**.**

* Includes ***adult and immature L4 stage***

Resistance may develop to any chemical. Ask your local veterinary practitioner or animal health adviser for recommended parasite management practices for your area to reduce development of resistance. It is advisable that a resistance test be conducted before any parasite treatment is used.

SAFETY TO SHEEP

The safety of this product has not been established in lambs less than 2 weeks of age or 10kg bodyweight. ZOLVIX has a wide margin of safety when used as recommended and is readily accepted by sheep. Pregnant and breeding sheep may be treated provided normal care is taken in handling.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, waterways or drains with the product or used containers. Do not discharge waste liquid into streams.

Disposal
The container can be recycled if it is clean, dry, free of visible residues and has the *drumMUSTER* logo visible. Triple or pressure rinse container for disposal. Dispose of rinsate or any undiluted chemical according to State legislative requirements. Wash outside of the container and the cap. Store cleaned container in a sheltered place with cap removed. It will then be acceptable for recycling at any *drumMuster* collection or similar container management program site. The cap should not be replaced but may be taken separately. DO NOT burn empty containers or product.

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

WARRANTY AND EXCLUSION OF LIABILITY
This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations or liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.

APVMA Approval No.
62752/2.5L/mmyy
62752/5L/mmyy
62752/10L/mmyy

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia **8.30 am to 5.30 pm E.S.T. Monday to Friday**

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

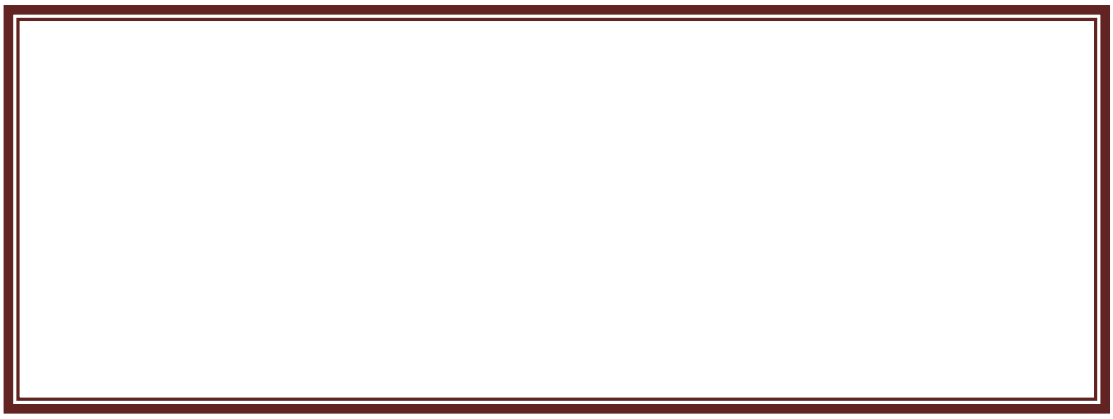
BAR CODE
DRUMMUSTER LOGO

Carton front panel: 2.5L, 5L, 10L

CAUTION
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel



2.5L, 5L, 10L

PICTOGRAM

NOVARTIS LOGO

Carton back panel: HDPE back label to be affixed on back panel of carton

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	1666	3333	6666
16–20	2.0	1250	2500	5000
21–25	2.5	1000	2000	4000
26–30	3.0	833	1666	3333
31–35	3.5	714	1428	2857
36–40	4.0	625	1250	2500
41–50	5.0	500	1000	2000
51–60	6.0	416	833	1666
61–70	7.0	357	714	1428
71–80	8.0	312	625	1250

Sheep in excess of 80 kg body weight should be dosed at 1 mL/10 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest sheep by liveweight in each group (ewes, wethers, rams, lambs). DO NOT under dose. Where there is a large variation in size within the group, dose rates should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. A correct drenching technique is recommended; carefully place the drench gun nozzle in the side of the mouth and over the back of the tongue before delivering the dose.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

ZOLVIX contains MONEPANTEL, a member of the new Amino-Acetonitrile Derivative class of anthelmintics that has a novel mode of action. It is effective against sensitive strains of the following internal parasites [Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***]** in sheep.

* Includes ***adult and immature L4 stage***

Resistance may develop to any chemical. Ask your local veterinary practitioner or animal health adviser for recommended parasite management practices for your area to reduce development of resistance. It is advisable that a resistance test be conducted before any parasite treatment is used.

SAFETY TO SHEEP

The safety of this product has not been established in lambs less than 2 weeks of age or 10kg bodyweight. ZOLVIX has a wide margin of safety when used as recommended and is readily accepted by sheep. Pregnant and breeding sheep may be treated provided normal care is taken in handling.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, waterways or drains with the product or used containers. Do not discharge waste liquid into streams.

Disposal
The container can be recycled if it is clean, dry, free of visible residues and has the *drumMUSTER* logo visible. Triple or pressure rinse container for disposal. Dispose of rinsate or any undiluted chemical according to State legislative requirements. Wash outside of the container and the cap. Store cleaned container in a sheltered place with cap removed. It will then be acceptable for recycling at any *drumMuster* collection or similar container management program site. The cap should not be replaced but may be taken separately. DO NOT burn empty containers or product.

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

WARRANTY AND EXCLUSION OF LIABILITY
This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations or liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.

APVMA Approval No.
62752/2.5L/mmyy
62752/5L/mmyy
62752/10L/mmyy

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia **8.30 am to 5.30 pm E.S.T. Monday to Friday**

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

® Registered trademark of Novartis AG, Basel, Switzerland.

BAR CODE
DRUMMUSTER LOGO

Aluminium pouch packsizes 0.25L, 0.5L and 1L

Pouch – Label front panel

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

0.25L, 0.5L, 1L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

Batch Number:	
Expiry Date:	

Pouch– – Label back panel

READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration
Use remaining product within 12 months of opening the container.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS
May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

APVMA Approval No.
62752/0.25LA/mmyy
62752/ 0.5LA/mmyy
62752/1LA/mmyy

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

BAR CODE

Multifolded zipseal leaflet for 0.25L, 0.5L, 1L (pouch)

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

0.25L, 0.5L, 1L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 0.25L	No. Treated/ 0.5L	No. Treated/ 1L	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	166	333	666	1666	3333	6666
16–20	2.0	125	250	500	1250	2500	5000
21–25	2.5	100	200	400	1000	2000	4000
26–30	3.0	83	166	333	833	1666	3333
31–35	3.5	71	142	285	714	1428	2857
36–40	4.0	62	125	250	625	1250	2500
41–50	5.0	50	100	200	500	1000	2000
51–60	6.0	41	83	166	416	833	1666
61–70	7.0	35	71	142	357	714	1428
71–80	8.0	31	62	125	312	625	1250

Sheep in excess of 80 kg body weight should be dosed at 1 mL/10 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest sheep by liveweight in each group (ewes, wethers, rams, lambs). DO NOT under dose. Where there is a large variation in size within the group, dose rates should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. A correct drenching technique is recommended; carefully place the drench gun nozzle in the side of the mouth and over the back of the tongue before delivering the dose.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

ZOLVIX contains MONEPANTEL, a member of the new Amino-Acetonitrile Derivative class of anthelmintics that has a novel mode of action. It is effective against sensitive strains of the following internal parasites [Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***]** in sheep.

* Includes ***adult and immature L4 stage***

Resistance may develop to any chemical. Ask your local veterinary practitioner or animal health adviser for recommended parasite management practices for your area to reduce development of resistance. It is advisable that a resistance test be conducted before any parasite treatment is used.

SAFETY TO SHEEP

The safety of this product has not been established in lambs less than 2 weeks of age or 10kg bodyweight. ZOLVIX has a wide margin of safety when used as recommended and is readily accepted by sheep. Pregnant and breeding sheep may be treated provided normal care is taken in handling.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, waterways or drains with the product or used containers. Do not discharge waste liquid into streams.

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

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

WARRANTY AND EXCLUSION OF LIABILITY
This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations or liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia **8.30 am to 5.30 pm E.S.T. Monday to Friday**

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

Carton front panel: 0.25L, 0.5L, 1L

CAUTION
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

0.25L, 0.5L, 1L

PICTOGRAM

NOVARTIS LOGO

Carton back panel: Pouch back label & multifolded leaflet to be affixed on back panel of carton

READ THE ATTACHED LEAFLET BEFORE USING THIS PRODUCT

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration
Use remaining product within 12 months of opening the container.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Storage

Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

APVMA Approval No.
62752/0.25LA/mmyy
62752/ 0.5LA/mmyy
62752/1LA/mmyy

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

BAR CODE

Aluminium pouch pack sizes 2.5L, 5L and 10L

Pouch – Label front panel

CAUTION

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel

Monepantel is a member of the new class of anthelmintics called the Amino-Acetonitrile Derivatives (AADs) and can be used for the treatment and control of AAD-sensitive strains of gastro-intestinal roundworms (nematodes), including macrocyclic lactone, benzimidazole (white), levamisole (clear) and morantel-resistant strains in sheep.

2.5L, 5L, 10L

READ DIRECTIONS FOR USE BEFORE USING THIS PRODUCT

Novartis Animal Health Australasia Pty Limited
ACN 076 745 198
54 Waterloo Road
North Ryde NSW 2113

NOVARTIS ANIMAL HEALTH LOGO

Batch Number:	
Expiry Date:	

Pouch– Label back panel

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	1666	3333	6666
16–20	2.0	1250	2500	5000
21–25	2.5	1000	2000	4000
26–30	3.0	833	1666	3333
31–35	3.5	714	1428	2857
36–40	4.0	625	1250	2500
41–50	5.0	500	1000	2000
51–60	6.0	416	833	1666
61–70	7.0	357	714	1428
71–80	8.0	312	625	1250

Sheep in excess of 80 kg body weight should be dosed at 1 mL/10 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest sheep by liveweight in each group (ewes, wethers, rams, lambs). DO NOT under dose. Where there is a large variation in size within the group, dose rates should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. A correct drenching technique is recommended; carefully place the drench gun nozzle in the side of the mouth and over the back of the tongue before delivering the dose.

Re-treatment Interval:
DO NOT re-treat less than 21 days after the last treatment. After three consecutive treatments, 115 days must elapse before treating again with ZOLVIX.

ZOLVIX contains MONEPANTEL, a member of the new Amino-Acetonitrile Derivative class of anthelmintics that has a novel mode of action. It is effective against sensitive strains of the following internal parasites [Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***]** in sheep**.**

* Includes ***adult and immature L4 stage***

Resistance may develop to any chemical. Ask your local veterinary practitioner or animal health adviser for recommended parasite management practices for your area to reduce development of resistance. It is advisable that a resistance test be conducted before any parasite treatment is used.

SAFETY TO SHEEP

The safety of this product has not been established in lambs less than 2 weeks of age or 10kg bodyweight. ZOLVIX has a wide margin of safety when used as recommended and is readily accepted by sheep. Pregnant and breeding sheep may be treated provided normal care is taken in handling.

WITHHOLDING PERIODS

MEAT: DO NOT USE less than 14 days before slaughter for human consumption.

MILK: DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

EXPORT SLAUGHTER INTERVAL (ESI): DO NOT USE less than 115 days before slaughter for export. The ESI on this label was correct at the time of label approval. Before using this product, confirm the current ESI from the manufacturer on 1800 633 768 toll free or the APVMA website (www.apvma.gov.au/residues/ESI.shtml).

SAFETY DIRECTIONS

May irritate the eyes. Will irritate the skin. Repeated exposure may cause allergic disorders. Avoid contact with eyes and skin. If product on skin, immediately wash area with soap and water. When using the product wear elbow length chemical resistant gloves. Wash hands after use. After each day's use wash gloves and contaminated clothing.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre (Phone 131126).

Material Safety Data Sheet

If additional hazard information is required, refer to the Material Safety Data Sheet. For a copy phone 1800 633 768.

Protection of Wildlife, Fish, Crustacea and Environment

Do not contaminate dams, waterways or drains with the product or used containers. Do not discharge waste liquid into streams.

Disposal
Triple rinse container before disposal. Dispose of rinsate or any undiluted chemical according to State/Territory legislative requirements. If not recycling, break, crush or puncture and deliver empty packaging to an approved waste management facility. Do NOT burn empty containers or product.

Storage
Store below 30^{o}C (Room Temperature). Store in the original tightly closed container. Use remaining product within 12 months of opening the container. Keep out of reach of children.

WARRANTY AND EXCLUSION OF LIABILITY
This product is warranted fit for the purposes specifically recommended by Novartis Animal Health Australasia Pty Limited when used strictly as directed on this label. All other warranties and obligations or liabilities, whether expressed or implied by statute or otherwise, are excluded to the full extent that exclusion is permitted by law.

APVMA Approval No.
62752/2.5LA/mmyy
62752/5LA/mmyy
62752/10LA/mmyy

☎ NOVARTIS CUSTOMER ASSISTANCE
1800 633 768 TOLL FREE from anywhere in Australia **8.30 am to 5.30 pm E.S.T. Monday to Friday**

NOVARTIS ANIMAL HEALTH AUSTRALASIA PTY LIMITED
54 Waterloo Road
North Ryde NSW 2113

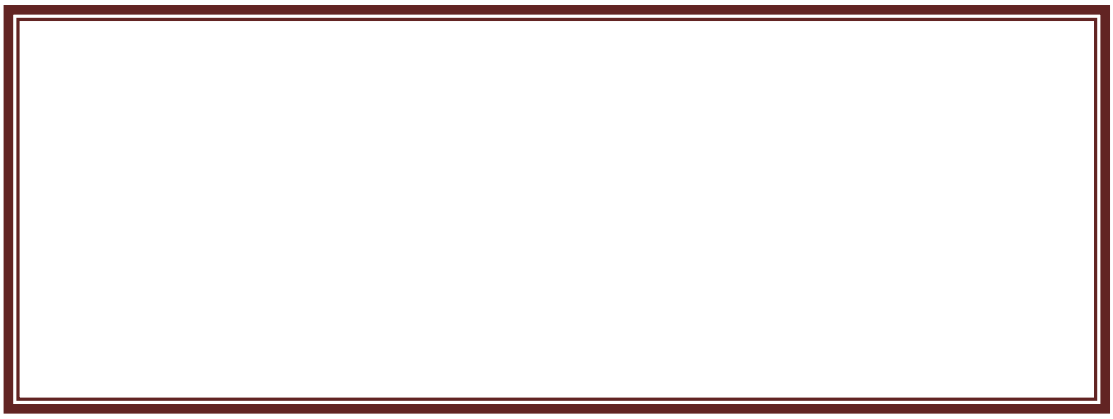
BAR CODE

Carton front panel: 2.5L, 5L, 10L

CAUTION
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING
FOR ANIMAL TREATMENT ONLY

ZOLVIX®
Monepantel
Broad Spectrum Oral Anthelmintic for Sheep

Active Constituent: 25 mg/mL Monepantel



2.5L, 5L, 10L

PICTOGRAM

NOVARTIS LOGO

Carton back panel: Pouch back label to be affixed on back panel of carton

ZOLVIX contains MONEPANTEL, a member of the new and unique class of anthelmintics, the Amino-Acetonitrile Derivatives (AADs). When used at the recommended dose rate (2.5 mg/kg), it is effective against AAD-sensitive strains of the following gastro-intestinal roundworms (nematodes) including those resistant to macrocyclic lactones, benzimidazoles (white drenches), levamisole and morantel (clear drenches) in sheep.

Efficacy spectrum (adult and/or immature L4 stage)

Barber's pole worm *Haemonchus contortus**, Small brown stomach worm *Ostertagia (Teladorsagia) circumcincta**, *Ostertagia (Teladorsagia) trifurcata**, *Ostertagia (Teladorsagia) davtiani* *, Black scour worm *Trichostrongylus colubriformis**, *Trichostrongylus vitrinus**, *Trichostrongylus rugatus**; Stomach hair worm *Trichostrongylus axei* *, Thin necked intestinal worm *Nematodirus filicollis**, *Nematodirus spathiger* (*adult only),* Small intestinal worm *Cooperia curticei* *, *Cooperia oncophora* *, Large mouthed bowel worm *Chabertia ovina**, Large bowel worm *Oesophagostomum venulosum* (*immature L4 only)***.**

* Includes ***adult and immature L4 stage***

DIRECTIONS FOR USE
Restraints:

DO NOT USE in sheep less than 10kg body weight.

DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Dosage and administration

Use remaining product within 12 months of opening the container. ZOLVIX is a ready-to-use solution. Check dose rates and drench gun before treatment commences. The dose is 0.5 mL/ 5 kg (1 mL/10 kg) ZOLVIX liveweight (equivalent to 2.5 mg MONEPANTEL/kg liveweight). Drench sheep orally, using a Novartis recommended drench gun. Maintain applicator gun carefully to ensure accurate dosage. After use, clean gun by flushing with warm, soapy water. Rinse with cold water.

Body weight (kg)	**Dose (mL)**	No. Treated/ 2.5	No. Treated/ 5L	No. Treated/ 10L
10–15	1.5	1666	3333	6666
16–20	2.0	1250	2500	5000
21–25	2.5	1000	2000	4000
26–30	3.0	833	1666	3333
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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ALP	alkaline phosphatase
ARfD	Acute Reference Dose (for humans)
ASAT	aspartate aminotransferase
ASCC	Australian Safety and Compensation Council
bw	bodyweight
d	day
EC_{50}	concentration at which 50% of the test population are immobilised
EMA	European Medicines Agency
ESI	Export Slaughter Interval
FAO	Food and Agriculture Organisation of the United Nations
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	hour
ha	hectare
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
HSIS	Hazardous Substances Information System
id	intradermal
im	intramuscular
ip	intraperitoneal
iv	intravenous
in vitro	outside the living body and in an artificial environment

in vivo	inside the living body of a plant or animal
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K_d	soil distribution coefficient
kg	kilogram
K_{oc}	organic carbon partitioning coefficient
L	litre
LC_{50}	concentration that kills 50% of the test population of organisms
LD_{50}	dosage of chemical that kills 50% of the test population of organisms
LOD	Limit of Detection – level at which residues can be detected
LOQ	Limit of Quantitation – level at which residues can be quantified
mg	milligram
mL	millilitre
MRL	Maximum Residue Limit
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NEDI	National Estimated Daily Intake
NESTI	National Estimated Short Term Intake
ng	nanogram
NOEC/NOEL	No Observable Effect Concentration / Level
PEC	Predicted Environmental Concentration
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell count

s	second
sc	subcutaneous
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TRR	Total Radioactivity Residue
µg	microgram
WHO	World Health Organisation
WHP	Withholding Period

GLOSSARY

Active constituent	The substance that is primarily responsible for the effect produced by a chemical product
Acute	Having rapid onset and of short duration.
Carcinogenicity	The ability to cause cancer
Chronic	Of long duration
Codex MRL	Internationally published standard maximum residue limit
Desorption	Removal of an absorbed material from a surface
Efficacy	Production of the desired effect
Formulation	A combination of both active and inactive constituents to form the end use product
Genotoxicity	The ability to damage genetic material
Hydrophobic	Water repelling
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octonol water partitioning co-efficient
Metabolism	The conversion of food into energy
Photodegradation	Breakdown of chemicals due to the action of light
Photolysis	Breakdown of chemicals due to the action of light
Subcutaneous	Under the skin
Toxicokinetics	The study of the movement of toxins through the body
Toxicology	The study of the nature and effects of poisons

REFERENCES

Australian Pesticides and Veterinary Medicines Authority 2008, *Vet MORAG: Manual of Requirements and Guidelines*, APVMA, Canberra.