Australian Government

Australian Pesticides and Veterinary Medicines Authority

PUBLIC RELEASE SUMMARY

on the Evaluation of the New Product STARTECT BROAD SPECTRUM ORAL DRENCH FOR SHEEP containing the New Active Derquantel

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Comments and enquiries regarding copyright:

The Manager, Public Affairs
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604 Australia

Telephone: +61 2 6210 4701
Email: communications@apvma.gov.au

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Revision history

The original version of this document was published on 14 August 2014.

Version 2 was published on 25 August 2014. On page 16, a table was deleted to clarify the dietary exposure estimates using a number of different approaches.

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PREFACE

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator 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, Office of Chemical Safety (OCS), Department of Environment, (DoE), and State Departments of Agriculture and Primary Industries.

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 products containing new active constituents.

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

This Public Release Summary is intended as a brief overview of the assessment that has been conducted by the APVMA and of the specialist advice received from 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, which may include details of:

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

Comment is sought from interested 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 *STARTECT® Broad Spectrum Oral Drench 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 matters include aspects of **public health, occupational health and safety, chemistry and manufacture, residues in food, environmental safety, trade,** and **efficacy and target crop or animal safety**. Submissions should state the grounds on which they are based. Comments received that address issues outside the relevant matters cannot be considered by the APVMA.

Submissions must be received by the APVMA by close of business on **12 September 2014** 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)
- email or postal address (if available)
- the date you made the submission.

All personal information, and confidential information judged by the APVMA to be ***confidential commercial information (CCI)***[1] 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:

enquiries
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604

Phone: +61 2 6210 4701
Fax: +61 2 6210 4741
Email: enquiries@apvma.gov.au

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

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: www.apvma.gov.au

1 INTRODUCTION

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has before it an application from Zoetis Australia Pty Ltd for registration of a new product, *STARTECT® Broad Spectrum Oral Drench for Sheep*, containing the new active constituent derquantel and the existing active constituent abamectin. This publication provides a summary of the data assessed and an outline of the regulatory considerations for the proposed registration of *STARTECT® Broad Spectrum Oral Drench for Sheep*.

Derquantel is the first member of the novel class of anthelmintics, the spiroindoles, and has a unique mode of action. Abamectin is a member of the macrocyclic lactone family.

STARTECT® Broad Spectrum Oral Drench for Sheep is an oral drench that contains 10 mg/mL derquantel and 1 mg/mL abamectin.

The proposed use is for the treatment and control of a broad range of susceptible adult and immature gastrointestinal nematodes of sheep, including those resistant to levamisole, benzimidazoles, macrocyclic lactones and closantel.

The proposed dose rate is 2mg derquantel and 0.2mg abamectin / kg bodyweight (1 mL *STARTECT*/5 kg bodyweight). *STARTECT® Broad Spectrum Oral Drench for Sheep* is administered as a single treatment. If repeat treatments are necessary, sheep are not to be retreated less than 28 days after the last treatment.

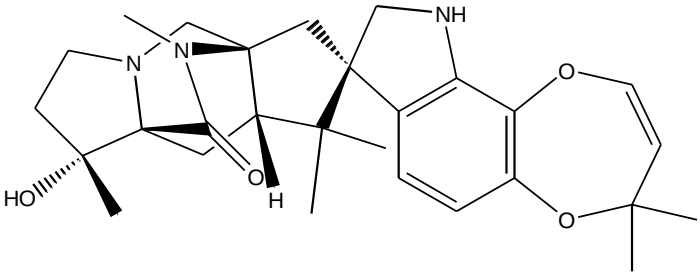
STARTECT® Broad Spectrum Oral Drench for Sheep will be packaged in 1L, 5L and 15L containers.

STARTECT® Broad Spectrum Oral Drench for Sheep is currently registered in UK, Ireland, New Zealand and South Africa.

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 derquantel has the following properties:

COMMON NAME (ISO):	Derquantel
CHEMICAL NAME (IUPAC):	(1'*R*,5'a*S*,7'*R*,8'a*S*,9'a*R*)-2',3',8a',9,9',10-hexahydro-1'-hydroxy-1',4,4,8',8',11'-hexamethyl-1',4*H*,5'*H*,6'*H*,8*H*,8'*H*-spiro[1,4-dioxepino[2,3-*g*]indole-8,7'-[5a,9a](iminomethano)cyclopenta[*f*]indolizin[10']one]
CHEMICAL NAME (CAS):	Spiro[4*H*,8*H*-[1,4]dioxepino[2,3-*g*]indole-8,7'(8'*H*)-[5*H*,6*H*-5a,9a](iminomethano)[1*H*]cyclopent[*f*]indolizin-10'-one, 2'3'8'a,9,9',10-hexahydro-1'-hydroxy-1',4,4,8',8',11'-hexamethyl-, (1'*R*,5'a*S*,7'*R*,8'a*S*,9'a*R*)-
PRODUCT NAME:	STARTECT BROAD SPECTRUM ORAL DRENCH FOR SHEEP
CAS REGISTRY NUMBER:	187865–22–1
EMPIRICAL FORMULA:	$C_{28}H_{37}N_3O_4$
MOLECULAR WEIGHT:	479.6 g/mol
PHYSICAL FORM:	powder
COLOUR:	white to tan
MELTING POINT:	254.4-226.0 °C
STRUCTURAL FORMULA:	

2.2 PRODUCT

Dose form: Oral drench

Formulation type: Non-aqueous solution

Level of actives: 10 g/L derquantel and 1 g/L abamectin

Physical properties – Appearance: The product is a clear to hazy, colourless to light yellow-brown 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 24 months when stored below 30 °C (room temperature) in the proposed commercial packaging. The product is shown to be unstable on exposure to low temperatures (below 0 °C) and a direction indicating this is on the product label.

Packaging

The product will be packaged in purple HDPE bottles with polypropylene caps contained in a cardboard carton (1 and 5 L) and purple HDPE drum with polypropylene cap (15 L) for the proposed product. Based on the storage stability results, 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 derquantel 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.

3 TOXICOLOGICAL ASSESSMENT

The Office of Chemical Safety (OCS) within the Department of Health has conducted the toxicology assessment of *STARTECT® Broad Spectrum Oral Drench for Sheep* containing 10 mg/mL derquantel and 1 mg/mL abamectin.

The toxicological database for derquantel 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.

Public Health Aspects & Toxicology Summary

Derquantel was rapidly absorbed and eliminated following oral dosing in rats. Due to the absence of a biliary study, the extent of gastrointestinal absorption could not be accurately estimated. It was extensively metabolised but none of the metabolites were identified. Most of the administered dose was excreted in faeces and to a much lesser extent, in urine. There is little evidence of accumulation based on toxicokinetic data in a one-year rat study by oral gavage at the highest dose level of 50 mg/kg bw/d, or in a 90-day dog study by oral gavage at the highest dose level of 5 mg/kg bw/d. There were no data available on dermal absorption or tissue distribution.

Derquantel has low acute oral, dermal and inhalational toxicity in rats. It was a slight eye irritant in rabbits, but was not a skin irritant in the same species. The maximisation test in guinea pigs was negative for skin sensitisation.

The product had low acute oral, dermal and inhalational toxicity in rats. It was a slight skin irritant in rabbits, but was not an eye irritant in the same species. The Buehler test in guinea pigs was negative for skin sensitisation.

Derquantel acts as a selective nicotinic antagonist in somatic muscle by competing for the ganglionic nicotinic cholinergic receptors. In repeat dose studies in dogs, clinical signs consistent with this mode of action (dry mouth, dilated pupils, droopy eyelid and relaxed nictitating membrane) were seen at all dose levels in a dose-dependent manner. The nicotinic antagonistic effects observed in dogs were not seen in rats. However, adverse neurological signs, including changes in behaviour and activity, reduced response to stimuli, the presence of fine tremors, altered posture and piloerection were seen in rats at higher dose levels compared to dogs.

Following repeat-dosing in rats, the primary target organ of derquantel was the liver and kidney. Increased severity of chronic progressive nephropathy (CPN) and biliary hyperplasia were seen in a one-year rat study. However, because CPN is a rodent-specific entity and there is no direct correlation between rat CPN and humans renal disease, increased risks of kidney tumour formation due to an exacerbation of CPN by derquantel is considered unlikely to be relevant for human health risk assessment.

Derquantel was neither a reproductive toxicant in rats nor a developmental toxicant in rats or rabbits, and is not an in vivo genotoxicant. No carcinogenicity studies were submitted. However, based on derquantel being a member of a chemical class (i.e. spiriondole) that is not known to be animal or human carcinogens, its genotoxicity profile, lack of significant pre-neoplastic lesions in a one year rat study and no indication from systemic toxicity studies that it may be linked with epigenetic mechanism of carcinogenicity that are relevant to humans, it is considered that dequantel does not pose a carcinogenic risk.

Occupational Health and Safety Summary

An occupational health and safety hazard assessment was performed by calculating the tolerable daily doses of derquantel and abamectin and then considering whether a worker's exposure would be likely to approach or exceed the tolerable daily dose. The OCSEH considers that it is likely that an unprotected worker would be exposed to the tolerable daily dose or more in a normal working day. Consequently, appropriate PPE has been recommended for acute risks to protect workers from skin irritation as well as systemic toxicity when using the product. No re-entry or re-handling statement is required for the product.

3.1 EVALUATION OF TOXICOLOGY

Toxicokinetics and Metabolism

Derquantel was rapidly absorbed and eliminated following oral dosing in rats, with maximum plasma levels observed between 0.5-4 h after administration in rats and dogs, and a plasma half-life of 2-7 h in rats. In rats, radiolabelled derquantel was excreted within 72 h, and was extensively metabolised. However, none of the metabolites were identified. Urinary excretion was 7%, and 88% was excreted in faeces, out of 95% total recovery. Due to the absence of a biliary study, the extent of gastrointestinal absorption could not be accurately estimated. In repeat dose studies in rats, the AUC and C_{max} were consistently higher in females than in males. In contrast, the AUC and C_{max} were generally higher in male than in female dogs. There is little evidence of accumulation based on toxicokinetic data in a one-year rat study by oral gavage at the highest dose level of 50 mg/kg bw/d, or in a 90-day dog study by oral gavage at the highest dose level of 5 mg/kg bw/d.

In vitro incubation of radiolabelled derquantel with hepatocytes and liver microsomes indicated that the major metabolites produced by dog hepatocytes and microsomes are more polar than those produced by rat, sheep, and human cells.

No dermal absorption or tissue distribution data were provided.

Acute toxicity studies

Derquantel has low acute oral (LD_{50} >1200 mg/kg bw), dermal (LD_{50} >2000 mg/kg bw) and inhalational toxicity (LC_{50} >2400 mg/m^3) in rats. The active constituent was a slight eye irritant in rabbits, but was not a skin irritant in the same species. The maximisation test in guinea pigs was negative for skin sensitisation.

The oral LD_{50} of the product was estimated to be 9005 mg/kg bw in female rats. The LD_{50} for dermal toxicity in rats was greater than 3045 mg/kg bw. The inhalational toxicity was also low in rats, with a 4-hr LC_{50} greater than 5040 mg/m^3. The product was a slight skin irritant in rabbits, but was not an eye irritant in the same species. The Buehler's test in guinea pigs was negative for skin sensitisation.

Short term and subchronic toxicity studies

Derquantel is a competitive nicotinic antagonist, which block nicotinic ganglionic stimulation of cells by competing for the ganglionic nicotinic cholinergic receptors. In repeat dose oral studies in dogs, clinical signs consistent with this mode of action (dry mouth, dilated pupils, droopy eyelid and relaxed nictitating membrane) were seen at all dose levels in a dose-dependent manner in a 28 day study, as well as in two 90-day studies at the lowest dose of 0.1 mg/kg bw/d. In the most recent 90-day study for which clinical signs consistent with derquantel's mode of action were not seen in control animals, relaxed nictitating membrane was noted at 0.1 mg/kg bw/d only on one occasion in one male and on three occasions in one female during the 90-day treatment period. In addition, dilated pupil was noted at 0.1 mg/kg bw/d on one occasion each in one male and one female. These clinical signs were generally noted within 2 hours of treatment and tended to disappear the following day. The evidence suggests that the LOEL dose of 0.1 mg/kg bw/d was approaching a threshold (or true NOEL). The nicotinic antagonistic effects observed in dogs were not seen in rats. In a 90-day study in rats, neurological assessment revealed adverse neurological signs at 50 and 150 mg/kg bw/d, including changes in behaviour and activity, reduced response to stimuli, the presence of fine tremors, altered posture and piloerection. There were no neurological findings at the next lower dose of 5 mg/kg bw/d.

Long term toxicity and carcinogenicity studies

Following repeat oral dosing in a 1-year rat study, the primary target organ of derquantel was the liver and kidney. Increased severity of chronic progressive nephropathy (CPN) and biliary hyperplasia were seen in a one-year rat study. Because CPN is a rodent-specific entity and there is no direct correlation between rats and humans, increased risks of tumour formation due to an exacerbation of CPN by derquantel are unlikely to be relevant for human health risk assessment.

No carcinogenicity studies were submitted with the current application. However, the carcinogenicity potential is considered to be low because**:**

- derquantel is not considered to be an *in vivo* genotoxicant (see below);
- is a member of the chemical class spiroindole that is not known to be animal or human carcinogens;
- there is a lack of significant preneoplastic findings in the one-year rat study; and
- systemic toxicity studies do not indicate that derquantel may be associated with effects known to be linked with epigenetic mechanisms of carcinogenicity that are relevant to humans

Reproduction and Developmental Studies

In an oral 2-generation reproduction study in rats, derquantel did not cause any reproductive or foetal toxicity at 25 mg/kg bw/d, the highest dose tested. Increases in implantation sites per delivered litter were noted at 25 mg/kg bw/d in the second generation females only. This was accompanied by increases in the total pups delivered at the same dose. Since there were no effects on other reproductive parameters and

these effects only occurred in the second generation, the significance of this increased fertility parameter is unclear. In the second generation the number of pups that were found dead, underwent unscheduled sacrifice or presumed cannibalised was increased at 1 and 25 mg/kg bw/d (7/341, 16/297, 5/286 and 13/344 at 0, 1, 5 and 25 mg/kg bw/d respectively) only on *post-partum* day 2-4 in the absence of a dose response. This finding was not considered to be treatment-related. The NOEL was 5 mg/kg bw/d for paternal toxicity and 25 mg/kg bw/d for both reproductive and foetal toxicity.

No teratogenic effect was observed in rat and rabbit developmental studies following oral administration. In rats, the maternal NOEL was 20 mg/kg bw/d, based on increased incidence of porphyrin discharge at the next higher dose of 70 mg/kg bw/d. The foetal NOEL was 70 mg/kg bw/d based on decreased pup body weight, and increased incidences of abnormal soft tissue and skeletal variations at the next higher dose of 120 mg/kg bw/d. In rabbits, the maternal and foetal NOEL was 1 mg/kg bw/d based on reduced bodyweight gain and food intake in does, and reduced foetal weight in females and an increased incidence of skeletal variations and resorptions at the next higher dose of 10 mg/kg bw/d. Thus, the foetal findings and resorptions are considered a secondary non-specific consequence of marked maternal toxicity.

Therefore, derquantel was neither a reproductive or developmental toxicant in these studies.

Genotoxicity Studies

Derquantel was negative for mutagenicity in a bacterial reverse mutation assay with and without metabolic activation. It was positive for inducing chromosomal aberrations in human peripheral lymphocytes in the presence and absence of metabolic activation. Dose-related increases were seen in both structural and numeric chromosome aberrations. There was a clear dose-related increase in polyploidy frequency (numeric aberration) at relatively non-cytotoxic doses. Increases in structural aberrations were seen only at dose levels which induced significant cytotoxicity. However, derquantel was negative in two micronucleus tests, one of which determined the incidence of micronuclei in the bone marrow of mice and the other its incidence in the liver of rats. Thus, the limited genotoxicity seen *in vitro* was not expressed *in vivo*.

Based on the weight of evidence derquantel is not considered to be an *in vivo* genotoxicant.

Neurotoxicity studies

No stand-alone neurotoxicity studies were submitted, but in several toxicity studies in rats and dogs, special tests such as for neurotoxicity were included. However, while no significant treatment related effects were seen on functional observation and motor activity parameters, clinical signs of neurotoxicity were clearly seen in acute oral and repeat oral dose studies, with the available data indicating that the dog is more sensitive than the rat to the neurotoxic properties of derquantel. In an acute oral study and 90-day oral study, dogs exhibited clinical signs of neurotoxicity from 5 mg/kg bw and 0.1 mg/kg bw/d respectively.

3.2 PUBLIC HEALTH STANDARDS

Poisons Scheduling

The delegate to the Secretary of the Department of Health and Ageing sought advice from the Advisory Committee on Chemical Scheduling (ACCS) on the scheduling of derquantel. Derquantel was discussed at the February 2011 meeting of the ACCS. The delegate noted and agreed with the recommendation of the ACCS that derquantel be included in Schedule 6 of the SUSMP. The delegate concluded that the case for a

cut-off from Schedule 6 for preparations containing 1 per cent or less of derquantel had not been established. The delegate's final decision made on 1st June 2011 confirmed that derquantel be included in Schedule 6 of the SUSMP with no cut-offs and an implementation date of 1 January 2012.

NOEL/ADI /ARfD

The Acceptable Daily Intake (ADI) is that quantity of an agricultural compound which 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 most sensitive toxicological end point that is most relevant to humans are clinical signs associated with the nicotinic antagonistic effects observed in dogs, which from the available data were the most sensitive species to derquantel. Thus, the ADI for derquantel was established at 0.0005 mg/kg bw/d based on a LOEL of 0.1 mg/kg bw/d in a 90-day dog study and using a 200-fold safety factor, as there is evidence to indicate that the LOEL of 0.1 mg/kg bw/d was approaching a threshold (or true NOEL) for the observed nicotinic antagonistic effects.

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 NOEL as a single or short-term dose which causes no effect in the most sensitive species of experimental animal tested, together with a safety factor which reflects the quality of the toxicological database and takes into account the variability in responses between species and individuals. The ARfD for derquantel was established at 0.01 mg/kg bw based on a NOEL of 1 mg/kg bw in an acute oral toxicity study in dogs and using a default 100-fold safety factor.

3.3 Conclusion

The registration of *STARTECT® Broad Spectrum Oral Drench for Sheep*, containing 10 g/L derquantel and 1 g/L abamectin for the control of nematode parasites in sheep by oral drench is supported

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4 RESIDUES ASSESSMENT

4.1 INTRODUCTION

Derquantel is a new anthelmintic, currently not registered for use in any animal species in Australia. Therefore, Maximum Residue Limits (MRLs) for derquantel 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).

The residues aspects of abamectin are also discussed below, in the context of existing MRLs, the withholding period and Export Slaughter Interval (ESI).

4.2 DATA PROVIDED

The Applicant provided details of metabolism studies that were conducted with derquantel in a range of animal species, including rats, dogs and sheep. Details of one total tissue residue decline study were provided, where [^{14}C]-derquantel was combined with abamectin in a commercially equivalent formulation. This study was utilized to establish the marker to total residue ratios, to recommend the Maximum Residue Limits (for derquantel) and to establish an appropriate withdrawal time for derquantel in the edible tissues of sheep. Additionally, two marker residue depletion studies were provided in which the first study confirmed the withdrawal time for derquantel relative to the recommended MRLs and the second study confirmed the withdrawal period for abamectin relative to its currently approved MRLs and Export Slaughter Interval.

4.3 EVALUATION SUMMARY

Metabolism of derquantel

Absorption

The metabolism studies show that derquantel is rapidly absorbed and distributed throughout the body after oral administration. Derquantel undergoes biotransformation to a large number of metabolites over a short period of time. However, the isolation and identification of all the metabolites was not possible. Derquantel (parent) consists of only a small percentage of the total residues in edible tissues.

The applicant proposed derquantel as the marker residue. Metabolism studies demonstrated that derquantel is extensively metabolized and represents only a small part of total residues. Despite this and in the knowledge that it is difficult to isolate and identify the metabolites of derquantel, the parent compound derquantel is considered to be a suitable marker residue for the purposes of setting a slaughter withholding period and for residue monitoring and surveillance.

Distribution

Derquantel is rapidly distributed throughout the body, and then undergoes rapid and extensive metabolism. When rats were administered single or multiple oral doses of ^{14}C-derquantel, approximately 1 % of the administered dose was retained in rat tissues at 48 hours after treatment.

When sheep were administered a single oral dose of 2.1 mg ^{14}C-derquantel/kg bw peak levels of radioactivity occurred at 6 hours after dosing, with highest total radioactive residues (TRRs) being 6.28 mg

equiv./kg in liver, 0.87 mg equiv./kg in kidney, 0.74 mg equiv./kg in fat, 0.26 mg equiv./kg in muscle, 0.28 mg equiv./kg in plasma and 0.21 mg equiv./kg in whole blood. Therefore, the relative rank order of derquantel TRRs in edible sheep tissues is: liver >>> kidney > fat >>> muscle.

Metabolism

Derquantel undergoes biotransformation to a large number of metabolites over a short period of time. The isolation and identification of all the metabolites was not possible. Derquantel, the parent compound, consists of only a small percentage of the total residues in edible tissues. There were no significant differences between the metabolic profile of derquantel in rat tissues and sheep tissues.

Excretion

Derquantel is excreted mainly in the faeces. When sheep were administered a single oral dose of 2 mg [^{14}C] derquantel/kg bw, recovery of the administered dose in urine, faeces and cage wash was rapid: approximately 50 % of the administered dose was recovered within 24 hours of dosing, and ~ 85 % of the dose was recovered within 48 hours of dosing. Most of the administered dose was recovered in the faeces.

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 derquantel in sheep is qualitatively similar to that determined in laboratory species (dogs and rats).

Summary

The metabolism studies show that derquantel is rapidly absorbed and distributed throughout the body after oral administration. The relative rank order of derquantel TRRs in edible sheep tissues is: liver >>> kidney > fat >>> muscle. Derquantel undergoes biotransformation to a large number of metabolites over a short period of time however, the isolation and identification of all the metabolites was not possible. Derquantel, the parent compound, consists of only a small percentage of the total residues in edible tissues. Most of the administered dose was recovered in the faeces.

Analytical method

Details were provided for a validated analytical method that could be used to determine derquantel residues in edible tissues from sheep. The validated analytical method was based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). The method involves derquantel being extracted from homogenised tissue samples with acetonitrile, subjected to additional purification on SPE cartridges, and analysed using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Practices relating to derquantel analysis were developed and implemented to control potential contamination issues, high background and matrix effects. These practices did not impact on method validation and the analytical method remains appropriate for the determination of derquantel residues in sheep tissues. The concentration of derquantel 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 used to determine the concentration of derquantel residues in sheep tissues 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	0.1	0.007
Muscle	0.1	0.022
Kidney	0.1	0.009
Fat	0.1	0.02

LOQ was set at the lowest validation control sample level used for the validation runs; the LOD was determined from concentration responses from at least 20 tissue blanks per matrix and according to the following formula: LOD = mean concentration response + (3 x standard deviation of the response).

Recoveries of derquantel were acceptable at the LOQ of 0.1 μg/kg.

In new studies provided by the manufacturer, all tissue samples were stored at -80^{o}C within 35 minutes of collection. Samples remained under these storage conditions, with the exception of the time stored at -20^{o}C to allow the dry ice to dissipate. The total time of storage at -20^{o}C was less than 31 hours for all samples.

The instability of derquantal tissue residues at -20^{o}C was further investigated. Aliquots of tissues collected at sacrifice were divided so that storage stability could be assessed at -20^{o}C and -80^{o}C. Derquantel marker residue assays were conducted approximately 4 months after sacrifice. A comparison of the data indicated that muscle tissue concentrations were decreased by average values of -57% (6 hour sampling timepoint), -8% (12 hour sampling timepoint) and -19% (1-day sampling timepoint) when stored at -20^{o}C relative to samples stored at -80^{o}C. For liver, kidney and fat samples, there were no significant differences in concentrations, indicating stability at -20^{o}C and -80^{o}C.

The conclusion is that tissue derquantel residues were stable under the storage conditions used in the new studies.

Residue definition

Metabolism studies demonstrated that derquantel is extensively metabolized and represents only a small part of total residues. In the knowledge that it is difficult to isolate and identify the metabolites of derquantel, the parent compound derquantel is considered to be a suitable marker residue for the purposes of setting a withholding period and for residue monitoring and surveillance.

Marker to total radioactive residues (TRRs) ratio

The total tissue residue study using [^{14}C]-derquantel combined with abamectin in a commercially equivalent formulation was used to calculate the marker (derquantel) to total radioactive residue ratios for derquantel. In this study, groups of animals were sacrificed at 12 hours, 1, 2, 4, 6, 8, 10, 14, 17, 21, 28, and 35 days after treatment. Samples of liver, kidney, muscle, subcutaneous fat and peri-renal fat were collected and stored frozen until analysed. The ratio results in liver, kidney, muscle and fat from sheep are presented below. Concentrations of derquantel residues rapidly depleted to <LOQ (0.1 μg/kg) in liver after Day 6; in kidney after Day 4; in muscle after Day 2; and in fat after Day 14. In addition, marker residue to total radioactive residues ratios could not be estimated in kidney after Day 10, or in muscle after Day 14. The data were used in an exposure assessment and to elaborate appropriate Maximum Residue Limits for derquantel.

Table 2: Derquantel marker residue to total radioactive residue ratios in tissues from sheep treated with [^{14}C]-Derquantel in a commercial equivalent formulation of STARTECT® *Broad Spectrum Oral Drench for Sheep*

Sampling Time (DAT)	Ratio of Marker Residue to Total Radioactive Residues (expressed as %)			
	Liver	Kidney	Muscle	Fat
0.25	11.2	36.2	29.0	61.1
0.5	9.85	24.9	24.4	54.4
1	5.61	16.1	19.9	49.6
2	2.23	4.76	1.46	32.4
3	0.991	2.05	0.403*	16.7
4	0.208	1.68	0.130*	7.34
6	0.115	0.076*	0.152*	5.15
10	0.057*	0.038*	0.296*	5.33
14	0.042*	n.e.	0.175*	4.03

Sampling Time (DAT)	Ratio of Marker Residue to Total Radioactive Residues (expressed as %)			
	Liver	Kidney	Muscle	Fat
24	0.004*	n.e.	n.e.	1.8*
35	0.027*	n.e.	n.e.	2.14*

Key: DAT = days after treatment; * Values have been calculated using marker residue concentration data <LOQ (0.1 μg/kg); n.e. = not estimable

Residues Trials

The applicant provided the total radioactive residue study (summarized above) one residues trial conducted with a commercially equivalent formulation of *STARTECT® Broad Spectrum Oral Drench for Sheep.* Sheep were administered a single oral drench of 3 mg derquantel/kg bw and 0.3 mg abamectin/kg bw (1.2× maximum dose rate). Derquantel (marker) residue depletion data were analysed using the EMA WT1.4 Meat Program for calculation of an appropriate withdrawal time using a data censoring approach. The analyses indicate that residues will deplete to below 0.2 μg/kg in liver at 8 days after treatment; in kidney at 6 days after treatment; in muscle at 3 days after treatment; and in peri-renal fat at 12 days after treatment.

A subsequent tissue marker residue decline study, confirmed that the recommended withdrawal time for derquantel was appropriate and consistent with the elaborated maximum residue limits in edible sheep tissues. In this study, the commercial formulation of *STARTECT® Broad Spectrum Oral Drench for Sheep* was administered orally to sheep at a dose rate of 2.5 mg derquantel/kg and 0.25 mg abamectin/kg body weight (1 mL/4 kg BW, 1.0x maximum dose rate). Groups of animals were sacrificed on days 0, 3, 10, 14, 24, 35, 45, 63, 77 post-treatment. In this study, no derquantel marker residue was present above the method LOQ by 10 days post treatment. Derquantel residue depletion data were analysed using the EMA WT1.4 Meat Program; a data censoring approach was taken. The analyses indicate that residues will deplete to below 0.2 μg/kg in liver at 14 days after treatment; in kidney at 12 days after treatment; in muscle at 8 days after treatment; and in peri-renal fat at 13 days after treatment.

In a previous marker residue study, the depletion of the appropriate abamectin marker residues was assessed for the purpose of confirming a withdrawal time and for assigning an ESI. The residues decline data indicate that abamectin residues in sheep liver, kidney, fat and muscle will comply with the Australian abamectin MRLs at 10, 7, 14 and 4 days after treatment, respectively.

The ESI endpoints were 25 μg/kg for sheep liver; 20 μg/kg for sheep kidney; 10 μg/kg for sheep muscle and sheep fat. The data from this study demonstrated that all abamectin residues had declined to the ESI endpoints by 28 days post treatment. The determinant for the ESI is abamectin, and comparable products (oral drenches in sheep) registered for use have ESIs of 28 days.

MRL recommendations

The following derquantel MRLs are recommended to cover the occurrence of derquantel residues in edible sheep tissues after the 14 day WHP has been observed: sheep muscle - 0.2 mg/kg; sheep fat – 0.2 mg/kg; sheep liver – 0.2 mg/kg; sheep kidney – 0.2 mg/kg.

Withholding period - Meat

Statistical analysis of the residues data indicates that derquantel residues in all edible sheep tissues will have declined to below the relevant recommended derquantel MRLs at 14 days after treatment. Statistical analyses of abamectin residues decline data concluded that abamectin residues in sheep liver, kidney, muscle and fat will comply with the Australian abamectin MRLs at 10, 7, 14 and 4 days, respectively, after dosing with *STARTECT®.* Therefore, a 14 day meat WHP is recommended for the use of *STARTECT®. Broad Spectrum Oral Drench 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 3.0 mg derquantel/kg bw and 0.3 mg abamectin/kg bw (1.2× maximum dose rate). A second residues trial was conducted where sheep were administered 2.5 mg derquantel/kg bw and 0.25 mg abamectin/kg bw. The applicant proposed a retreatment interval for 28 days for *STARTECT® Broad Spectrum Oral Drench for Sheep*. As the Applicant did not provide any residue data following animal re-treatment, the APVMA policy of assigning a re-treatment interval equivalent to the time for the marker residue to decline to its LOQ was applied.

Table 3: The Limits of Quantification (LOQs) and Limits of Detection (LODs) for the concentration of Abamectin B1a/ Abamectin B1b residues in sheep tissues

Analyte	Tissue matrix	LOQ (μg/kg)	LOD (μg/kg)
Abamectin B_{1a}	Liver	10	0.08
	Kidney	10	0.43
	Muscle	10	0.05
	Fat	10	0.61
Abamectin B_{1b}	Liver	0.66	0.02
	Kidney	0.66	0.01
	Muscle	0.66	0.02
	Fat	0.66	0.02

The LOQs for abamectin B_{1a} and abamectin B_{1b} in liver, kidney, muscle and fat are presented above. Data indicate that residues of abamectin B_{1a} are <LOQ at 21, 28 and 35 days after dosing. All tissues with the exception of muscle tissue were below LOD at 21, 28 and 35 days after dosing. Muscle tissues which were above the LOD were below the LOQ of the analytical method (10 μg/kg) with the highest value recorded at day 28 of 0.3 μg/kg. Data indicate that residues of abamectin B_{1b}, with two exceptions, are <LOD in liver, kidney, muscle and fat at 17, 21, 28, and 35 days after dosing. The exceptions involve liver tissue collected on days 17 and 21 after dosing, which had abamectin B_{1b} residues of 0.23 μg/kg and 0.36 μg/kg, respectively, which are above the reported LODs for those tissues. As these concentrations are less than the LOQ of the analytical method (0.66 μg/kg), the depletion of abamectin B_{1b} is consistent with a retreatment interval of 28 days.

Derquantel marker residue was shown to deplete to less than LOQ by the withholding period of 14 days in all tissues. Therefore as abamectin is the determinant residue, its decline to LOQ defines the re-treatment interval for *STARTECT® Broad Spectrum Oral Drench for Sheep*.

A retreatment interval of 28 days as proposed by the applicant is therefore supported.

Dietary risk assessment

Dietary exposure assessment

Attempts to calculate an estimated daily intake (EDI) were unsuccessful on account of there being insufficient data to establish median residues for derquantel. Therefore the theoretical maximum daily intake (TMDI) approach was used. The TMDI calculation using the model diet and the marker to total radioactive residues ratio approach was calculated. Derquantel MRLs of 0.2 μg/kg for sheep liver, kidney, muscle and fat, result in an estimated dietary exposure of 4.23 μg/person of 60 kg bw, which represents approximately 14.1% of the upper bound of the ADI on Day 2 after dose administration.

At the proposed WHP (using TRR at 14 days), the chronic exposure estimate using FSANZ consumption figures is less than 5% of the ADI, and the acute dietary exposure to derquantel in sheep liver, kidney, muscle and fat is less than 1% of the acute reference dose for each tissue.

Statistical analyses of abamectin residues decline data concluded that abamectin residues in sheep liver, kidney, muscle and fat will comply with the Australian abamectin MRLs at 10, 7, 14 and 4 days, respectively, after dosing with *STARTECT*®.

4.4 CONCLUSIONS AND RECOMMENDATIONS

Registration of the product

The Veterinary Residues Team (VRT) and independent reviewers have evaluated the residues aspects of *STARTECT*® *Broad Spectrum Oral Drench for Sheep.* The Reviewers have considered available data, including, metabolism, residue trials, analytical methodology, fate in storage, processing data and residues in trade issues, including that submitted by Zoetis Australia Pty Ltd to support their application to register a new oral product for use in sheep.

It has been recommended 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 APVMA supports the following label instructions for *STARTECT*® *Broad Spectrum Oral Drench for Sheep*:

ANIMAL	PURPOSE	DOSE RATE
Sheep	For the treatment and control of intestinal nematodes including those resistant to levamisole, benzimidazoles, macrocyclic lactones and closantel.	Nominal: 1 mL product/5 kg bw (i.e. 2 mg/kg derquantel and 0.2 mg/kg abamectin 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 28 days after the last treatment.

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 USE less than 28 days after treatment before slaughter for export.

Recommended amendments to the MRL standard

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

Table 4: MRL Standard - Table 1 Recommendations

Table 1 COMPOUND	FOOD	MRL (µg/kg)
ADD:		
	Sheep muscle	0.2
	Sheep fat	0.2
	Sheep kidney	0.2
	Sheep liver	0.2

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 *STARTECT® Broad Spectrum Oral Drench 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

Zoetis Australia Pty Ltd has indicated that *STARTECT® Broad Spectrum Oral Drench for Sheep* is registered in the UK, Ireland, New Zealand and South Africa.

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.

Codex MRLs have not been established for derquantel in sheep tissues. The European Union has established derquantel MRLs as follows: sheep liver 0.02 mg/kg; sheep kidney 0.005 mg/kg; sheep muscle 0.002 mg/kg; and sheep fat 0.04 mg/kg. Derquantel MRLs in sheep tissues have not been established by the USA, China, Japan and CIS.

In the pivotal tissue marker residue decline study, no derquantel was present above the method LOQ by the withholding period of 14 days post treatment. The depletion of the appropriate abamectin marker residues was assessed for the purpose of assigning an ESI. The ESI endpoints were 25 μg/kg for sheep liver; 20 μg/kg for sheep kidney; 10 μg/kg for sheep muscle and sheep fat. The pivotal tissue marker residue decline study demonstrated that all abamectin residues had declined to the ESI endpoints by 28 days post treatment. The determinant for the ESI is abamectin, and comparable products (abamectin-containing oral drenches for sheep) registered for use have ESIs of 28 days.

Conclusion

Overall, the risk to Australia's export trade in sheep commodities is considered to be low when the recommended ESI of 28 days is observed for *STARTECT® Broad Spectrum Oral Drench for Sheep*.

The APVMA proposes 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 derquantel and abamectin 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 28 days is observed.

6 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Health hazards

Derquantel is not listed as a hazardous substance on the on Safe Work Australia's HSIS Database (SWA, 2010). With the available toxicology information, OCSEH has determined that derquantel is classified as a hazardous substance according to the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004), with the following risk phrase:

R48/22	Danger of serious damage to health by prolonged oral exposure

Derquantel has a neurotoxic potential, and has produced clinical signs of toxicity in both dogs and rats in repeated dose oral studies. In a 90 day repeat oral study in rats, adverse neurological signs (such as changes in behaviour and activity, reduced responses, fine tremors and altered posture) were observed in animals at 50 mg/kg bw/day, with effects seen in dogs at lower concentrations. The observed effects justify classification with Xn; R48/22.

The following cut-off concentration applies for derquantel:

Conc. ≥ 10%	Xn; R48/22

The other active ingredient in the formulation, abamectin, is listed on Safe Work Australia's HSIS Database (SWA, 2010) with the following risk phrases:

R26/28	Very toxic by inhalation or if swallowed
R24	Toxic in contact with skin
Repr. Cat. 3; R63	Possible risk of harm to the unborn child
R23/25	Toxic by inhalation or if swallowed
R21	Harmful in contact with skin
R20/22	Harmful by inhalation or if swallowed

The following cut-off concentrations apply for abamectin:

Conc. $\geq$ 25 %	T^+; R26/28, R24, R63
7 % $\leq$ Conc. < 25 %	T^+; R26/28, R21, R63
5 % $\leq$ Conc. < 7 %	T; R23/25, R21, R63
3 % $\leq$ Conc. < 5 %	T; R23/25, R21
1 % $\leq$ Conc. < 3 %	T; R23/25
0.1 % $\leq$ Conc. < 1 %	Xn; R20/22

Based on the studies conducted on the product and the concentrations of the actives (1% derquantel, 0.1% abamectin) and the nature of the other ingredients in the product, the product *STARTECT® Broad Spectrum Oral Drench for Sheep* would be classified as a hazardous substance in accordance with NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004) with the following risk phrase:

Xn; R48/22	Danger of serious damage to health by prolonged oral exposure

Formulation, packaging, transport, storage and retailing

STARTECT® Broad Spectrum Oral Drench for Sheep will be formulated overseas as a ready-to-use product and supplied in 1 L, 5 L HDPE backpack or 15 L jerrycan HDPE containers fitted with polypropylene caps. Transport workers and store persons will handle the packaged products and could only become contaminated if packaging is breached.

6.1 Use pattern

STARTECT® Broad Spectrum Oral Drench for Sheep will be used to control nematode parasites in sheep by oral drench. Workers would use a drench gun attached via a delivery tube to a container worn as a backpack by the operator. The solution is administered orally over the base of the tongue around 1-2 times per year. A single oral dose of the product will be administered to sheep at a dose rate of 1 mL per 5 kg bw.

Exposure during use

Farmers and their employees will be the main users of the product. Workers may become contaminated with the product during application, loading the backpack, cleaning up spills and maintaining equipment. The main route of exposure to the product will be dermal, though ocular exposure may also occur. Inhalational exposure is considered unlikely.

There are no exposure studies on derquantel or the product. Further, there are no accepted models or experimental data for determining acquired systemic doses when using the product as proposed. In the absence of these studies or models, an occupational health and safety hazard assessment was performed by calculating the tolerable daily doses of derquantel and abamectin and then considering whether a worker's exposure would be likely to approach or exceed the tolerable daily dose. The OCS considers that it is likely that an unprotected worker would be exposed to the tolerable daily dose or more in a normal working day. Consequently, appropriate PPE has been recommended for acute risks to protect workers from skin irritation as well as systemic toxicity when using the product.

Exposure during re-entry

There is no risk associated with re-entry with *STARTECT® Broad Spectrum Oral Drench for Sheep*.

Recommendations for safe use

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

6.2 Conclusion

The registration of *STARTECT® Broad Spectrum Oral Drench for Sheep*, containing 10 g/L derquantel and 1 g/L abamectin for the control of nematode parasites in sheep by oral drench is supported.

STARTECT® *Broad Spectrum Oral Drench 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 on the product MSDS.

7 ENVIRONMENTAL ASSESSMENT

7.1 INTRODUCTION

Zoetis Australia Pty Ltd has applied for registration of a new product, *STARTECT®. Broad Spectrum Oral Drench for Sheep*, containing an existing active constituent (ac) abamectin (1 mg/mL) and a new active constituent derquantel (10 mg/mL). The proposed treatments for the control of gastro-intestinal nematodes in sheep are to be administered orally via drench guns at the application rate of 0.2 mL product/kg bw, corresponding to 2 mg derquantel/kg bw and 0.2 mg abamectin/kg bw.

7.2 ENVIRONMENTAL CHEMISTRY AND FATE

Abiotic Degradation

Derquantel contains no hydrolysable groups based on its chemical structure and thus it is expected to be stable under normal environmental conditions. Based on the UV spectral data in acidic, neutral and basic methanol, it is expected that derquantel will not be directly photodegradable.

Biodegradation

Aerobic soil metabolism

The aerobic soil metabolism of [^{14}C]-derquantel was studied in sandy loam, clay loam and silty clay loam soils at an application rate of ca 70 µg/kg soil under aerobic conditions. At the end of the studies the mean recovery (mass balance) of applied radioactivity (AR) from the sandy loam soil ranged from 95-101%. Levels of solvent extractable radioactivity declined from 96% of the AR at 0 time to 31% at day 120. The amount of evolved $^{14}CO_2$ remained low throughout the study, accounting for 2% of AR at termination. ^{14}C volatiles (≤ 0.11%) were negligible throughout the incubation period. Non-extractable residues, which accounted for 4% AR at 0 time, increased as the incubation period progressed, reaching a maximum of 68% of AR at day 120. Similar observations were made in clay loam and silty clay loam soils where $^{14}CO_2$ and ^{14}C volatiles remained low throughout the incubation period and the levels of non-extractable residues increased with a corresponding decrease in extractable residues levels as the incubation period progressed.

Analysis of the sandy loam extract at 0 time by LC-MS confirmed the presence of at least 8 components. Derquantel was the major component present and represented 63% of AR on day 0; none of the other components detected accounted for >10% AR. On day 4, at least seven components were present and levels of derquantel had declined to 20% of AR. By Day 16, at least eight components were present, none of which corresponded to derquantel. Some were >10% AR but could not be identified due to instability and/or weak spectrometric signals. No derquantel was detected in either the clay loam or the silty clay loam extracts due to the rapid degradation in these soils.

Chromatographic analysis by radio-HPLC and HPLC-MS confirmed that derquantel was rapidly and extensively degraded following administration to soils. Based on the disappearance of parent from the soils, the DT50 values for derquantel were estimated as <4 days in sandy loam and <1 day in clay loam and silty clay loam. Therefore, derquantel will rapidly degrade and not persist in soils.

Mobility

Soil adsorption/desorption studies

Adsorption/desorption of radiolabelled derquantel was determined in three different soil types (silt loam, sandy loam and clay loam). A quantitative balance of radioactivity was established. The adsorption constants (K_d) in the three test soils ranged from 22.80-39.73 mL/g and the corresponding adsorption coefficient (K_{oc}) values were 622-1840 mL/g. Based on McCall's Mobility Classifications, derquantel is considered to be of low mobility in these three soils. Desorption of derquantel from the three different soil types was relatively low over the 24 h period and the adsorption process is considered to be only partially reversible.

Bioaccumulation in aquatic organisms

In accordance with VICH Phase II guidance, Tier B testing for bioconcentration in fish should be considered if the log $K_{ow} \geq 4$. Thus, based on the log K_{ow} of 2.96 for derquantel, Tier B testing is not required. Additionally, derquantel is not expected to be bioaccumulative based on the extensive metabolism in sheep.

7.3 ENVIRONMENTAL EFFECTS

Aquatic organisms

Acute toxicity studies of derquantel on rainbow trout (96 h EC50 = 57.5 mg ac/L), *Daphnia magna* (48 h EC50 = 21.17 mg ac/L), algae (72 h EbC50 = 24.7 mg ac/L) and marine diatom (96 h EC50 = 55 mg ac/L) indicate that derquantel is slightly toxic to these species. A chronic study indicates that derquantel is moderately toxic (21 days NOEC = 0.044 mg/L) to *Daphnia magna*.

Non-target Invertebrates (Terrestrial)

Earthworms

The 56 days EC50 based on reproduction was estimated to be 170 mg ac/kg dry weight, indicating a slight toxicity to earthworms. The 56 days EC10 was determined to be 54 mg ac/kg dry soil.

Dung Flies

The EC50 was estimated to be 1.38 mg ac/kg fresh dung based on % juvenile mortality for derquantel, indicating derquantel is toxic to dung flies. The NOEC in dung was determined by DSEWPaC to be 0.26 mg ac/kg fresh dung.

Dung Beetles

The LC50 and NOEC for 1st generation adult mortality was 64.6 mg/kg fresh dung and 4.0 mg/kg fresh dung, respectively. The EC50 and NOEC for the emergence of 2nd generation adults was 19.3 mg ac/kg fresh dung and 4.0 mg ac/kg fresh dung, respectively.

Soil Microorganisms

Derquantel did not have an impact on soil microflora based on the soil nitrogen transformation at a concentration of up to 0.14 mg ac/kg dry soil. It is concluded that the active constituent does not have a long term influence on soil nitrogen transformation.

Phytotoxicity

Derquantel did not show any effects on seedling emergence for perennial ryegrass, winter wheat, soybean, radish and tomato at concentrations of 1.0, 10.0 and 100.0 mg/kg dry soil. Significant adverse effects on weight were observed for radish and tomato at 1 and 10 mg/kg dry soil, respectively, and for other plants at higher concentrations. The LC50 and EC50 were determined to be >100 mg/kg dry soil for each of the species tested. The NOEC was determined to be <1 mg/kg soil based on weight for radish and tomato.

7.4 PREDICTION OF ENVIRONMENTAL RISK

Birds, mammals and reptiles

The oral drench application of derquantel to sheep will result in little if any exposure to birds, mammals and reptiles.

Aquatic organisms

The department of environment's 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. As the toxicity of abamectin predominates over derquantel, the risk assessment was conducted based primarily on the most sensitive end point, *Daphnia magna* for abamectin in the aquatic compartment, though the presence of derquantel was also considered in the proposed product.

On the basis of $PEC_{surface\ water}$ and the most sensitive end-point for abamectin, the ultimate risk quotient is calculated to be mitigable. Given that abamectin is expected to partition strongly to faeces and sediment of the aquatic environment, it is expected that the amount available in the water will be significantly less. It is concluded it is unlikely that abamectin, together with derquantel, will pose an unacceptable risk as a result of discharge of faeces directly into a stream.

A 0.1 % and 1% run-off for abamectin and derquantel, respectively, as a result of rainfall flowing into a pond in a feedlot scenario result in low concentrations of the active constituents 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.

Non-target invertebrates and micro-organisms

The PEC in the terrestrial compartment under Australian farm practices was estimated to be 2.05 and 20.5 µg ac/kg dry soil for abamectin and derquantel, respectively, in a feedlot scenario based on 100% of the excreted drug as parent compound.

The proposed use of the product under Australian farm practices is not expected to present unacceptable risks to earthworms and soil micro-organisms. This is based on studies showing that the calculated PECs are well below the toxicological end points tested.

The risks of the proposed product to dung beetles and dung flies under Australian conditions are mitigated by the fact that sheep faeces is not a preferred resource for these species due to the pelletised morphology.

Non-target vegetation

Abamectin is essentially non-phytotoxic, permitting its use even on sensitive ornamental plants. While plants will emerge successfully, at the soil concentration of 20.5 µg ac/kg dry soil for derquantel, some retardation in growth of plants cannot be ruled out following the spread of manure on agricultural land. However, there is nearly a 50-fold safety factor when compared to the NOEC of <1 mg/kg and adverse effects on plant growth are unlikely to occur from the proposed use of the product.

7.5 CONCLUSION

The proposed administration of *STARTECT® Broad Spectrum Oral Drench for Sheep* to sheep is unlikely to pose an unacceptable environmental risk under the proposed use pattern.

In order to be satisfied that the proposed uses of the product will not lead to an unintended effect that is harmful to animals, plants or things, or to the environment at the proposed rate and following good agricultural practice, DoE has recommended amendments to the draft label's warning and container disposal statements.

8 EFFICACY AND SAFETY ASSESSMENT

Derquantel is a new anthelmintic to the Australian market, and belongs to the spiroindole class of anthelmintics. The product, *STARTECT®. Broad Spectrum Oral Drench for Sheep*, contains 10 g/L derquantel and 1 g/L abamectin as the active ingredients.

The proposed claims are for the treatment and control of a broad range of susceptible adult and immature gastrointestinal nematodes of sheep, including those resistant to levamisole, benzimidazoles, macrocyclic lactones and closantel.

STARTECT®. Broad Spectrum Oral Drench for Sheep will be administered at 2mg derquantel and 0.2 mg abamectin / kg bodyweight (1 mL STARTECT/5 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 trial designs, treatment group sizes, ages and types of animal used, experimental conditions, administration of test and reference products, sample collection and analysis of data were generally appropriate for establishing the efficacy and margin of safety of the test product under normal use conditions for treatment and control of gastrointestinal nematode parasites and lungworm in sheep.

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.

In a dose titration trial conducted in Merino hoggets the test product showed excellent efficacy against *H. contortus, T. colubriformis, and T. circumcincta* at 0.25X, 0.5X and 1X the proposed use dose.

In six trials conducted in Australia, New Zealand, South Africa and the UK in sheep harbouring natural infections of susceptible strains of mixed gastrointestinal nematodes and lungworm, the test product was effective against *H.contortus, T. circumcincta* (adult & hypobiotic L4), *T. trifurcata, T. axei, T. colubriformis, T. vitrinus, N.spathiger, C. curticei, C. surnabada, S. papillosus, O. venulosum and D. filarial.*

In two trials conducted in Australia and New Zealand in sheep harbouring artificial infections of mixed gastrointestinal nematodes, the test product was highly effective against the L4 larval stages of *H. contortus, Tel. circumcincta, Tel. trifurcata, T. axei, T. colubriformis, T. vitrinus,* and *C. curticei.*

In three trials conducted in Australia in Merino lambs and hoggets harbouring artificial infections of multi-resistant strains of gastrointestinal nematodes, the test product was highly effective against *H. contortus, Tel. circumcincta* and *T. colubriformis.*

In seven field studies conducted on commercial farms in NSW, Victoria and WA in sheep harbouring naturally acquired mixed strongyle burdens, with *Nematodirus* and lungworm present in some animals, the test product was highly effective against *Haemonchus* spp., *Teladorsagia* spp., *Trichostrongylus* spp., *Nematodirus* spp., *Oesophagostomum* spp., *Dictyocaulus filaria* and *Chabertia* spp., and was safe when administered under field conditions.

Claims for the following nematode species and stages are supported, when the product is used at the proposed label dose rate of 1mL *STARTECT®. Broad Spectrum Oral Drench for Sheep* 5kg bodyweight providing a dose rate of 2mg derquantel and 0.2mg abamectin / kg liveweight.

Haemonchus contortus (adult and immature L4);

Trichostrongylus axei (adult and immature L4);

Teladorsagia (*Ostertagia) circumcincta* (adult and immature L4 including inhibited L4 stages);

Teladorsagia (*Ostertagia) trifurcata* (adult and immature L4);

Trichostrongylus colubriformis (adult and immature L4);

Trichostrongylus vitrinus (adult and immature L4);

Cooperia curticei (adult and immature L4);,

Cooperia oncophora (adult and immature L4);

Cooperia surnabada (adult and immature L4);

Nematodirus spathiger (adult);

Strongyloides papillosus (adult and immature L4);

Oesophagostomum venulosum (adult);

Chabertia ovina (adult);

Trichuris ovis (adult);

Dictyocaulus filaria. (adults only)

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

8.2 EVALUATION OF TARGET ANIMAL SAFETY DATA

In two target animal safety studies in sheep administered doses of 1X, 3X and 5X the maximum recommended dose of 0.3 ml / kg of the test product on multiple occasions, adverse CNS clinical signs and deaths were observed in several animals after the 5X dose. There were no other toxicological changes associated with the test product in any of the clinical parameters measured in terms of clinical pathology, body weight, feed intake or pathology end points. It was concluded that 0.3 ml/kg body weight be considered the maximum dose of the test product.

In pre-ruminant lambs administered doses of 1X, 2X and 3X the maximum recommended dose of 0.3 ml / kg and in 9-13 week old lambs administered a single dose of 0.3 ml/ kg repeated 14 days later, no abnormal clinical symptoms or adverse events were recorded that could be attributed to the test product other than a transient coughing immediately after treatment in up to 76% of animals. Under normal use conditions in lambs aged from 6 weeks, *STARTECT®. Broad Spectrum Oral Drench for Sheep* has acceptable tolerance and safety in the event of over-dosage.

In a reproductive safety trial in female sheep administered 3X the nominal dose rate (1ml /5kg body weight) on multiple occasions throughout the reproductive cycle, the test product was clinically well tolerated, and no effects were observed on any aspect of breeding, gestation, lambing, lactation, or lamb growth and caused no teratogenicity.

In a reproductive safety trial in male sheep administered 3X the nominal dose rate (1ml /5kg body weight) of the test product on three occasions throughout the spermatogenic cycle, there was no discernable effect on sperm quality, libido, body condition and condition of the reproductive organs.

8.3 CONCLUSIONS

Under normal use conditions, *STARTECT®. Broad Spectrum Oral Drench for Sheep* is effective for the treatment and control of adult and immature larval (L4) stages of gastrointestinal nematodes and lungworm, including those resistant to levamisole, benzimidazole, macrocyclic lactone and closantel drenches and has an acceptable margin of safety in the event of over-dosage.

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

LABELLING REQUIREMENTS

POISON
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

STARTECT®

Broad Spectrum Oral Drench for Sheep

10 mg/mL DERQUANTEL
1 mg/mL ABAMECTIN

For the treatment and control of a broad range of susceptible adult and immature gastrointestinal nematodes of sheep, including those resistant to levamisole, benzimidazoles, macrocyclic lactones and closantel.

1 L/5 L/15 L

Zoetis [logo]

IMMEDIATE CONTAINER LABEL
BACK PANEL

Startect contains derquantel and abamectin in combination. Derquantel is the first member of the novel class of anthelmintics, the spiroindoles, and has a unique mode of action. Abamectin is a member of the macrocyclic lactone family.

Startect is effective against adult and immature (L4) stages of sensitive strains of the following internal parasites, including those resistant to levamisole (LEV), benzimidazoles (BZ), macrocyclic lactones (ML) and closantel (CLOS): .

Barber's pole worm *Haemonchus contortus*; Stomach hair worm *Trichostrongylus axei*; Small brown stomach worm *Teladorsagia* (*Ostertagia) circumcincta* including inhibited (L4) stages, *T. trifurcata*; Black scour worm *Trichostrongylus colubriformis*, *T. vitrinus*; Small intestinal worm *Cooperia curticei, C. oncophora; C. surnabada*; Thin-necked intestinal worm *Nematodirus spathiger**; Intestinal threadworm *Strongyloides papillosus*; Large bowel worm *Oesophagostomum venulosum**; Large mouthed bowel worm *Chabertia ovina**; Whipworm *Trichuris ovis**; Lungworm *Dictyocaulus filaria.* (* adults only).

Startect was demonstrated to be highly effective against multi-resistant strains of *Haemonchus contortus* (LEV, BZ, ML and CLOS) and *Teladorsagia circumcincta* and *Trichostrongylus colubriformis* (both LEV, BZ and ML).

Resistance may develop to any drench. 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 drench resistance test be conducted before any drench is used.

DIRECTIONS FOR USE
Restraints
DO NOT RE-TREAT for 28 days after last treatment .
DO NOT USE in female sheep which are producing or may in the future produce milk or milk products for human consumption.

Precautions
Very toxic to horses. Do not use in horses or species other than sheep.
Estimate liveweights carefully to avoid overdosing. Acute toxicity and deaths have occurred at doses greater than three times the recommended dose.
Shake container before use.

DOSE RATE - 1 mL/5kg bodyweight. Dose by mouth.

Bodyweight kg	Dose mL	1 L Treats	5 L Treats	15 L Treats
15	3	333	1666	5000
16 - 20	4	250	1250	3750
21 - 25	5	200	1000	3000
26 - 30	6	166	833	2500
31 - 35	7	142	714	2142
36 - 40	8	125	625	1875
41 - 45	9	111	555	1666
46 - 50	10	100	500	1500
51 - 55	11	90	454	1363
56 - 60	12	83	416	1250
61 - 65	13	76	384	1153
66 - 70	14	71	357	1071
71 - 75	15	66	333	1000

Animals in excess of 75 kg to be dosed at 1 mL/5 kg. A representative sample of animals should be weighed before treatment. Dose the mob to the heaviest animal by liveweight in each group (ewes, wethers, rams, lambs). Do not underdose. Where there is a large variation in size within the group, dose rate should be based on the label directions for each weight range. Drafting into two or more lines may be appropriate, to avoid excessive overdosing. Use drench gun with silicone sealed 'o' rings.

Safety: The safety of this product has not been established in lambs less than 6 weeks of age or 15 kg bodyweight. A high proportion of sheep may cough following treatment. This passing response is of no consequence. Studies have shown no adverse effects on reproduction in breeding animals dosed at three times the recommended rate.

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 28 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 814 883 or the APVMA website (www.apvma.gov.au/residues/).

SAFETY DIRECTIONS
May irritate the skin. Avoid contact with the skin. When opening the container and using the product, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and elbow-length chemical-resistant gloves. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use wash contaminated clothing.

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

Additional information is in the Safety Data Sheet (SDS).

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND THE ENVIRONMENT
Very toxic to aquatic life. Do not contaminate dams, rivers or streams with the product or used container.

DISPOSAL: Triple rinse containers before disposal. Dispose of rinsate or any undiluted chemical according to State 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°C (Room temperature). Do not expose to temperatures below 0°C. Discard product that separates or contains sediment following exposure to temperatures below 0°C. Protect from direct sunlight.

APVMA Approval Number: 64247/47910

Batch:. Expiry:

[Zoetis logo]

Made in New Zealand
Zoetis Australia Pty Ltd
Level 6, 5 Rider Blvd,
Rhodes NSW 2138

CARTON FOR 1L, 5L

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READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

STARTECT®

Broad Spectrum Oral Drench for Sheep

10mg/mL DERQUANTEL
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For the treatment and control of a broad range of susceptible adult and immature gastrointestinal nematodes of sheep, including those resistant to levamisole, benzimidazoles, macrocyclic lactones and closantel.

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66 - 70	14	71	357
71 - 75	15	66	333

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Level 6, 5 Rider Blvd,
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ABBREVIATIONS

ac	active constituent
ADI	Acceptable Daily Intake (for humans)
ai	active ingredient
ARfD	Acute Reference Dose
AUC	Area Under Curve
bw	bodyweight
C_{max}	Maximum concentration
CPN	Chronic Progressive Nephrotrophy
d	day
DAT	Days After Treatment
DT_{50}	Time taken for 50% of the concentration to dissipate
EA	Environment Australia
E_bC_{50}	concentration at which the biomass of 50% of the test population is impacted
EC_{50}	concentration at which 50% of the test population are immobilised
EDI	Estimated Daily Intake
EEC	Estimated Environmental Concentration
E_rC_{50}	concentration at which the rate of growth of 50% of the test population is impacted
EI	Export Interval
ESI	Export Slaughter Interval
EUP	End Use Product
Fo	original parent generation
g	gram
GAP	Good Agricultural Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVP	Good Veterinary Practice

h	hour
Hct	Heamatocrit
HDPE	High Density Polyethylene
Hg	Haemoglobin
HPLC	High Pressure Liquid Chromatography *or* High Performance Liquid Chromatography
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 Expert Committee on Food Additives
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

NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration Level
OCSEH	Office of Chemical Safety and the Environment
OM	Organic Matter
po	oral
ppb	parts per billion
PPE	Personal Protective Equipment
ppm	parts per million
Q-value	Quotient-value
RBC	Red Blood Cell Count
s	second
sc	subcutaneous
SC	Suspension Concentrate
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAC	Technical grade active constituent
TMDI	Theoretical Maximum Daily Intake
TRR	Total Radioactive Residues
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
µg	microgram
vmd	volume median diameter
VRT	Veterinary Residues Team
WG	Water Dispersible Granule
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 a material from or through 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	repels water
Leaching	Removal of a compound by use of a solvent
Log Pow	Log to base 10 of octanol water partitioning co-efficient, synonym KOW
Metabolism	The chemical processes that maintain living organisms
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.