SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

The active substance of ZOLVIX is monepantel, which is an anthelmintic belonging to the amino-acetonitrile derivative (AAD) class of molecules. Monepantel acts on the nematode specific nicotinic acetylcholine receptor sub-unit Hco-MPTL-1. ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes. The route of administration is oral use. The target species is sheep. The approved indication is:

"ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes. Spectrum of activity includes fourth larvae and adults of: *Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcata,Teladorsagia davtiani, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus vitrinus, Cooperia curticei, Cooperia oncophora, Nematodirus battus, Nematodirus filicollis, Nematodirus spathiger, Chabertia ovina, Oesophagostomum venulosum.* The veterinary medicinal product is also effective against strains of these parasites resistant to (pro)benzimidazoles, levamisole, morantel and macrocyclic lactones."

2. QUALITY ASSESSMENT

Composition

The formulation is a clear 25 mg/ml, yellow to orange oral solution.

Qualitative Composition	Quantitative composition (per ml)	Reference to analytical quality
Active Substance(s) Monepantel Form B (parent compound)	25.0 mg	Novartis testing monograph
Other ingredients		
all-rac-alpha-Tocopherol (*Antioxidant*)		Ph.Eur.*
30% Beta-Carotene dispersion in corn oil (*Colouring agent*)		Novartis testing monograph
Propylene glycol (*Co-solvent*)		Ph.Eur.*
Macrogolglycerol hydroxystearate (*Surfactant*)		Ph.Eur.*
Polysorbate 80 (*Co-surfactant*)		Ph.Eur.*
Propylene glycol monocaprylate (*Co-solvent*)		Novartis testing monograph
Propylene glycol dicaprylocaprate (*Solvent*)		Ph.Eur.*

* Current Edition.

The composition is adequately described and the functions of the excipients are indicated and references to standards are provided.

Container

The finished product is packed into multidose containers. The pack sizes are 0.25 l, 0.5 l, 1 l, 2.5 l, and 5 l. The primary packaging is either a laminated aluminium bag or a fluorinated HDPE bottle.

Alu Bag: laminated aluminium foil, heat-sealed to form a bag. The HDPE spout is sealed between the front and back foils and covered with a polypropylene cap.
HDPE bottle: fluorinated high density polyethylene bottle with induction heat-sealed polypropylene cap.

Clinical Trial Formula(e)

Details of the compositions of the clinical trial formulations and the clinical studies performed for each of the batches were provided. The final proposed formulation for the non-aqueous oral solution has been used in clinical efficacy, dose confirmation, target animal safety, and field efficacy and safety studies. The colouring agent beta-carotene has been used in order to provide a distinction from other market products.

Development Pharmaceutics

The active ingredient Monepantel has shown efficacy against intestinal nematodes in sheep. For sheep the common route of application is by oral drenching, therefore a solution or suspension for this kind of application was developed. The final formulation is a non-aqueous solution which has been characterized to be self-emulsifying when added to water. The final formulation is a clear, orange solution containing 25 mg Monepantel per ml of the solution.

Components of the product

Active substance
During development compatibility of the active substance with regard to excipients was investigated during preliminary stability studies.

The active substance N-[(1S)-1-Cyano-2-(5-cyano-2-trifluoromethyl-phenoxy)-1-methylethyl]-4-trifluoromethylsulfanyl-benzamide with INN name Monepantel is a white powder which is practically insoluble in water, slightly soluble in propylene glycol and n-octanol, soluble in ethanol and freely soluble in polyethylene glycol 300 and dichloromethane. Monepantel is a very lipophilic compound and is non-hygroscopic; no water-uptake is observed between 30% RH and 90% RH.

Polymorphism: Basic investigations on the crystal form revealed that two crystal forms, form A and form B exist. Form B is the thermodynamically most stable form at room temperature and the form used in the formulation.

Isomerism: The active ingredient is the S-enantiomer which has been separated from the R-enantiomer.

Excipients

All excipients used in the formulation are standard excipients and meet the requirements of the Ph. Eur. with the exception of Propylene glycol monocaprylate and Beta-carotene 30% FS. Propylene glycol mono- and diesters in a content of max 31 % fulfils the requirements of E 477 for food additives.

Beta-carotene 30% FS was added to provide distinction from other marketed products and thereby avoid mix-ups compromising drug safety. Pure beta-carotene is not available in large quantities;

therefore a 30 % suspension in corn oil was chosen. To protect beta-carotene from oxidation the use of anti-oxidant is required and several anti-oxidants were tested during development. Alpha-Tocopherol was found to be the most suitable.

Formulation Development

Suspensions
In early development studies suspensions of the active substance were prepared. The water containing solutions and suspensions froze when subjected to temperatures below 0 ˚C, and later development work was focused on non-aqueous solutions. Efficacy data were also in favour of the non-aqueous solutions.

Solutions
Propylene glycol monocaprylate was chosen as co-solvent and beta-carotene was chosen as colouring agent.

Preservatives were added and, in order to enhance solubility of preservatives and stabilise alpha tocopherol and beta-carotene, also propylene glycol. During testing of antimicrobial preservative efficacy it was demonstrated that a formulation containing at least 1 % propylene glycol was self-preserved and addition of preservatives was not necessary. This was further confirmed by results of ongoing primary stability studies.

The function and choice of excipients for the final formulation proposed for marketing were outlined.

Summary of tests performed during development

- Microbiological testing

The final formulation passed the criteria for oral products according to Ph. Eur. 5.1.3. Having self-preservative properties the absence of antimicrobial preservative is justified.

- Stability studies
    - Stability of the active substance, Monepantel in the final formulation was investigated by short term stress studies in glass vials for 12 months at 8 ˚C, RT, 30 ˚C, 40 ˚C and for 6 months 50 ˚C; as well as at 40˚C/75% RH and 25˚C/60% RH for 12 months in HDPE bottles. The content of the active substance and colour of the solution was determined during the storage period. No changes were observed.
    - Stability of beta-carotene in placebo formulations containing different antioxidants; butyl hydroxytoluene, alpha tocopherol, octyl gallate, propyl gallate and benzyl alcohol for 12 months at 8 ˚C, RT, 30 ˚C, 40 ˚C and 50 ˚C in glass vials. The optimal anti-oxidant was found to be alpha-tocopherol in a concentration of 0.05% w/v.
- Integrity of drench-gun O-rings and outlet checks.

Interactions of the solvent with O-rings in the drench-gun leading to leaks, blocks and incorrect volume are well known. Therefore several commercial O-rings and outlet checks were examined after two weeks exposure to different formulations. Formulations containing Transcutol (diethylene glycol monoethyl ether) or Labrasol (caprylocaproyl macrogolglycerides) could influence functionality and Transcutol was therefore replaced by propylene glycol monocaprylate.

Packaging Material

The fluorinated HDPE bottle was chosen and subjected to stability. Additionally; aluminium bags with a Ph. Eur compliant PE layer provide an optimal barrier for solvent and were also chosen for stability studies.

Manufacturing Process

The manufacturing process consists of dissolving the active substance in the placebo formulation.
The steps comprising the process are outlined below:

- Beta-carotene is dissolved in propylene glycol dicaprylocaprate

- The other liquid excipients propylene glycol, all-rac-alpha-tocopherol, polysorbate 80 and propylene glycol monocaprylate are added and the solution is mixed.
- Macrogolglycerol hydroxystearate is molten in a separate vessel, added to the solution and mixed again.
- The active ingredient is added and the solution is stirred until the active ingredient is completely dissolved.

An engineering batch was prepared in order to optimize stirring/dissolving time. Based on the results obtained for this batch, stirring time was set but is to be confirmed during process validation. A final filtration is performed to clarify the solution and it was demonstrated that the filter did not adsorb the active substance during filtration. Three batches, which all conformed to the finished product release specification, were manufactured and the homogeneity of the batches was examined by analysis of the content of the active substance in the beginning, middle and end of the filling process.

METHOD OF PREPARATION

Manufacturing Formula and Batch Size

Batch sizes are selected according to seasonal demands. The manufacturing formula was described in detail.

Manufacturing Process and In-process Controls

The manufacturing process is a standard process consisting of the preparation of a solution followed by filling into appropriate containers.

A flow-chart outlining the manufacturing process was provided along with details of the in-process controls performed.

Validation of Manufacturing Process

The manufacturing process is a conventional and well established process used in the pharmaceutical industry for the manufacture of solutions. The process comprises three major steps:

- Mixing and dissolution of excipients
- Addition and dissolution of the active substance
- Bulk solution filtration and filling into containers

Several pilot scale batches have been manufactured and filled into multi-dose bags and bottles.

Status
The manufacturing process will be validated prior to distribution and sale for three consecutive production scale batches. Validation will be performed according to established validation protocols.

The critical parameters of the manufacturing process identified during pilot scale up validation and production validation of the investigational veterinary material are:

- Mixing time until complete dissolution of the active substance
- The potential adsorption of the active substance on the filter during bulk filtration

CONTROL OF STARTING MATERIALS

Active Substance
Full documentation for the active substance was provided by the applicant.

Specification and routine tests

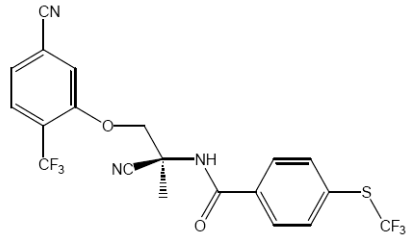
Active ingredients listed in a Pharmacopoeia.
Not applicable.

Active ingredients not listed in a Pharmacopoeia.
The active substance specification is composed like a monograph with the specifications outlined in detail in the documentation provided. The analytical methods used for testing are described in connection with the specification and representative spectra and chromatograms are provided in connection with the description of the methods. The structures of related substances are included as well as a change history.

Scientific data

Nomenclature
INN Name: Monepantel
IUPAC Name : *N*-[(1S)-1-Cyano-2-(5-cyano-2-trifluoromethyl-phenoxy)-1-methyl-ethyl]-4-trifluoromethylsulfanyl-benzamide
CAS RN : 887148-69-8

Description



Molecular Formula: $C_{20}H_{13}F_6N_3O_2S$
Relative Molecular Mass: 473.39
Chirality: The active substance has one chiral centre and possesses two enantiomers: the active (*S*)-enantiomer (parent compound A) and the inactive (*R*)-enantiomer which is considered an impurity.

Synthetic route

A flow-chart of the overall synthesis is provided. In addition a flow-scheme for each step is provided containing detailed information about all unit operations within each step. These flow schemes also contain information about the reagents and solvents used and the yield of each step, where appropriate. The manufacture is a three step synthesis followed by chromatographic resolution of the racemate into two enantiomers.

Quality control during manufacture

Starting materials:
The analytical methods applied for testing of the starting materials have been properly described and validation data for the methods have been presented. The methods applied for determination of impurities have been validated with respect to specificity/selectivity, precision and LOD (Limit of Detection), which is considered adequate since both are limit tests.

Adequate specifications have been set for the reagents and solvents used in the synthesis. Control tests on critical steps and intermediate products were described. The analytical methods applied for analysis of the intermediates have been properly described.

Development Chemistry

Evidence of structure
Proof of structure has included IR, NMR (^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR, gs-DQF-COSY, ROESY, APT, gs-HSQC), elemental analysis and FIA-MS. The absolute configuration of the chiral centre has been determined by X-ray structure analysis. The results are consistent with the assigned structure.

Potential isomerism and polymorphism
Two polymorphic forms have been disclosed and characterized. Both forms are considered to be ansolvates. Form B is the most stable form at room temperature. Form A melts at about 125 °C and form B, which has a melting point of 148 °C, crystallizes from the melt on subsequent heating. The two different forms can be distinguished by their XRPD patterns. Due to the fact that form A is easily converted into form B it is recommended not to prepare and use form A in formulations.

Physico-chemical characterisation
The substance is practically insoluble in water and pH and pKa –values are therefore considered irrelevant; however a suspension in water 10 g/L has a pH of 6.2-6.3. Melting range: 142 -149 °C. Log P was calculated to 3.0. The solubility in different solvents at 20 °C was described.

The choice of analytical methods applied for testing of the active substance was described and is based on the chemical structure of the molecule. Test methods and specifications are in compliance with pharmacopoeia monographs where relevant.

Reference material
The analytical master standard has been characterised by ^{1}H-NMR, XRPD, elemental analysis and analysis for purity, water content, residual solvents, sulphated ash and melting range has been performed.

The standard used for relevant impurity has been characterised by ^{1}H-NMR, elemental analysis and analysis for purity, water content, residual solvents and sulphated ash has been conducted.

Validation of analytical methods
The GC method has been validated with respect to specificity, stability of sample solutions, linearity range, accuracy, precision (repeatability), LOD/LOQ (Limit of Quantification) for the solvents ethanol, methanol, and methylcyclohexane.

The chiral HPLC method has been validated with respect to specificity, accuracy, precision (for both enantiomers), intermediate precision, linearity and range, LOD, LOQ, stability of sample solution.

The achiral HPLC method used for assay and impurities has been validated with respect to specificity, accuracy, precision, intermediate precision, linearity and range, LOD and LOQ.

The microbial limit test has been validated (pour plate method) according to the previous Ph. Eur. editions and validation data for the newly harmonised method will be provided subsequently.

Forced degradation studies
Forced degradation studies have been performed and representative chromatograms were provided.

Justification of specifications

The limits are justified by reference to pharmacopoeial requirements and EU/VICH guidelines and are acceptable.

Impurities

Potential impurities were described in detail, including their structure, origin, proposed limit, maximum level seen according to batch analysis and LOD/LOQ.

Batch analysis
Batch analysis data for a number of batches were provided as well as certificates of analysis for each batch. Batch analysis results for batches used in toxicity and efficacy studies were also provided. The batch analysis results comply with the specifications and confirm the consistency of the product.

Reference material:
Details were provided of the reference material for the active substance, Monepantel, as well as related substances.

Excipients

Specifications and routine tests

Excipients described in a Pharmacopoeia

Macrogol hydroxystearate, polysorbate 80, all-rac-tocopherol, propylene glycol, propyleneglycol dicaprylocaprate are all described in Ph. Eur. and comply with the respective monographs.

Excipient(s) not described in a Pharmacopoeia

Beta-carotene 30 % FS and propylene glycol monocaprylate are not described in any pharmacopoeia. The individual excipients comprising beta-carotene 30 % FS are however all described in Ph. Eur. Propylene glycol monocaprylate is classified as a food additive.

Scientific data

Certificates of analysis were provided for all excipients.

Regarding the composition of beta-carotene, a declaration of compliance with Ph. Eur. for each of the constituents was provided, as well as a certificate of analysis. The Applicant's testing specification was also provided.

Propylene glycol monocaprylate

Testing specifications for propylene glycol monocaprylate were provided in addition to a certificate of analysis and IR spectrum.

Packaging Material (Immediate Packaging)

Specifications and routine tests

Active substance
The active substance is stored in drums lined with polyethylene liners. The polyethylene liners in contact with the active substance comply with EU Directive 2002/72/EC and amendments and a statement of compliance was presented from the supplier. A specification containing ID (IR) is presented and a representative IR spectrum was enclosed.

Finished product
The finished product is packed into laminated aluminium foil heat-sealed to form a bag containing a spout covered with a tamper evident polypropylene screw cap or in fluorinated HDPE bottles with induction heat sealed caps.
Specifications for the laminated aluminium bag and the fluorinated HDPE bottles containing ID (IR) were enclosed. A specification, including ID (IR), for the screw cap was also presented.

Scientific data

Finished product
Declarations of compliance with the food-stuff regulation, EU Directive 2002/72/EC for the polyethylene resin used for the fluorinated HDPE bottles, and compliance with FDA food-stuff regulations for the screw cap were provided. The polyethylene used as lamination in the Alu bags comply with Ph. Eur. 3.1.3, and the polypropylene used for the cap comply with Ph. Eur. 3.2.2. Applicant's certificates of analysis were enclosed.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHY

Declarations were enclosed from excipient suppliers, active substance- and finished product manufacturers confirming either that none of the materials used in the manufacture and primary packaging of the finished product are of animal or human origin and/or are in compliance with the EU guideline *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal product* (EMEA/410/01-Rev.2).

CONTROL TESTS ON INTERMEDIATE PRODUCTS

Not applicable.

CONTROL TESTS ON FINISHED PRODUCT

Product Specification and Routine Tests:

Product specifications and tests for release at time of manufacture (general characteristics, specific standard)

The specification applies at release and during shelf-life. If different specifications limits are defined at release than during shelf-life it is indicated. Tests performed were described.

Control methods

Test procedures for identification and quantitative determination for the active substance(s)

Two independent methods, TLC and HPLC are applied for ID of the active substance. The HPLC method applied for ID is also used for determination of assay and degradants.

Identification and determination of excipient(s)

The colouring agent beta-carotene is identified by TLC. The anti-oxidant alpha-tocopherol is identified by HPLC and this method is also used for determination of the content of alpha-tocopherol.

Safety tests

Individual and total amounts of related substances are determined by HPLC. Microbial purity is tested at release and followed during stability, in terms of efficacy of antimicrobial preservation test, for the first three full-scale production batches.

Scientific Data

Analytical validation of methods and comments on the choice of routine tests and standards

A reverse-phase HPLC method is used for the determination of assay Monepantel and related substances in final product. The enantiomeric purity of several available solutions, stored for up to 12 months in fluorinated HDPE bottles at 40°C/75% RH, has been examined and no racemisation of the active substance was observed. Enantiomeric purity is not considered a stability indicating parameter and therefore stereospecific testing is not included in the finished product specification. The specification limits for individual degradants are set at the identification/qualification threshold of 1.0 % according to the CVMP/VICH guideline VICH GL11: Impurities in new veterinary medicinal products CVMP/VICH/838/99-Rev.1.

Validation of the analytical methods

The TLC methods applied for identity of beta-carotene and Monepantel have been validated with respect to specificity. The two TLC methods are able to differentiate beta-carotene and Monepantel

from colorants and active substances (respectively) commonly used at Novartis' manufacturing sites. The HPLC method applied for determination of identity and content of alpha-tocopherol has been validated with respect to accuracy, precision (repeatability and intermediate precision), linearity, range, robustness, specificity, LOD, LOQ and stability of calibration and sample solutions. The HPLC method applied for determination of identity and content of Monepantel and degradants has been validated with respect to specificity, accuracy, precision (repeatability and intermediate precision), linearity, range, robustness, LOD and LOQ.

A dosing device is not enclosed; however it has been demonstrated that doses corresponding to the posology can be withdrawn with commonly used dosing devices and in compliance with Uniformity of mass of delivered doses in Ph. Eur.

Batch analyses
Batch analysis results were presented from pilot batches. Batch analysis has been performed according to the testing instruction in force at the time of release. At that time no tests for alpha-tocopherol ID or content existed. Therefore the results for testing of these parameters are not available. All the submitted results comply with the proposed specification limits and confirm the consistency of the product. Batch analysis results from batches used in target animal studies were also provided.

STABILITY

Stability Tests on the Active Substance(s)
The applicant proposes the following re-test period/storage condition: 3 years/no special precautions for storage, when stored in 100 µm thick PE bags within a metal drum.

Batches investigated:
A number of pilot scale batches were placed on stability.

Parameters investigated: Assay, enantiomeric purity, content of impurities, total content of impurities, appearance, and loss on drying, X-ray diffraction (performed at highest temp. at every time point).

Results: No significant changes were observed. All parameters comply with the specification limits. The stability results allow a re-test period of 3 years on the basis of extrapolation.

Stress testing:

One pilot batch was subjected to stress testing. No significant changes were observed. Tests were also performed in solution/suspensions at room temperature and photostability light stress testing. The results were satisfactory.

Stability Tests on the Finished Product
The applicant proposes the following shelf life/storage condition:
36 months/no special precautions for storage for the fluorinated HDPE bottles
24 months/no special precautions for storage for the laminated aluminium bags.

In-use stability: Use within 12 months after opening.
The proposed shelf-lives are acceptable.

Stability Tests

Batches investigated: 3 pilot scale batches, packed in white fluorinated HDPE bottles or Aluminium bags (representing the range of pack sizes), were placed on stability. Parameters were, unless otherwise indicated tested according to the testing frequency described in EU/VICH GL3 guideline "Stability testing of new Veterinary Drug Substances and Medicinal Products".

All results remain within the specification limit throughout the storage period. No significant changes were observed. There do not seem to be any differences in stability related to pack sizes and/or packaging material.

Photostability: Light stress testing has been performed on a laboratory batch of the finished product.

All results remained within specification limit throughout the exposure period. No changes were observed in assay and enantiomeric purity compared to the unexposed samples. Minor variations in the amount of impurities are observed. It was concluded that the product is not susceptible towards photolytic degradation and no special precautions concerning protection form light is necessary.

The stability results with the 1 l and 2.5 l fluorinated HDPE bottles allow a shelf-life of 36 months on the basis of extrapolation of 24 month stability results. The stability results of 250 ml and 5 l Alu bags -representing the extremes in filling volume- allow a shelf-life of 24 months based on extrapolation of 12 month stability data. For both packaging the Applicant has committed to continue the ongoing registration stability tests with finished product until the end of the proposed shelf life and to conduct a stability study with the first three commercial batches of finished product according to the same protocol as the one used for the registration batches

In-use Stability Tests

A number of half-emptied 1 l HDPE bottles, and partly emptied 250 ml Alu bags were subjected to stability studies. All results remained within specification limit throughout the storage period. Assay values varied, no special trend was observed. Two related substances were observed, one of them is the synthesis by-product and the other a degradation product. The amount of impurities varies and no special trend is observed. The applicant has committed to provide results from a second in-use stability test with a batch approaching the end of its shelf life

Supplementary information concerning analytical methods used during development was provided.

OVERALL CONCLUSION ON QUALITY

The overall impression is of scientifically sound and well written documentation with a focus on the essential aspects of active substance properties and the impact on the performance and quality of the finished product. The documentation demonstrates a comprehensive knowledge of the active substance and the finished product and the documentation is presented in a systematic way, identifying the rationales for further development or discarding of a possible formulation.

Manufacturing of the finished product has been properly described. Pre-validation data for the manufacturing process are provided. The manufacturing process of the active substance has been adequately described. Specifications for the active substance and the finished product have been set in line with current guidelines. The provided stability data demonstrates good stability of both the active substance and the finished product.

3. SAFETY ASSESSMENT AND RESIDUES

Identification of the product concerned by the Application

International non-proprietary name (INN)	monepantel
Classification Therapeutic	Nematodicide
Pharmacological	
Synonyms and abbreviations	The parent compound is the active S- enantiomer of NG-96 NG-96 is the racemic mixture of the R- and S- enantiomers
Degree of impurity	<3 % (specified)
Qualitative and quantitative composition of impurities	N-[2-(5-cyano-2-trifluormethyl-phenyloxy)-1-(S)-1-cyano-1-methyl-ethyl]-4-chloro-benzoic amide, residual solvents etc, each specified at ≤0.5 %
Description of physical properties: Melting point:	125 °C (form A), 142-149°C (form B)
Vapour pressure:	2.8 x 10^{-11} hPa (at 25°C - extrapolated value)
Solubility in water	0.08 mg/l at 20°C
Solubility in organic solvents, at 25°C	dichlormethane: 175 g/l ethanol: 60.7 g/l n-octanol: 7.3 g/l propylene glycol: 6.9 g/l polyethylene glycol: 156.1 g/l
Density	1.468 g/cm3
*Octanol / water partition coefficient (*log K_{ow})	4.7 (QSAR estimate)

Pharmacological Studies

Pharmacodynamics

Special pharmacology

The compound has a very rapid, potent, and penetrant neuromuscular effect on *Caenorhabditis elegans*. The mode of action on nematodes has been studied using a forward genetic screen for resistant *Caenorhabditis elegans* mutants. Of 44 resistance alleles isolated, 36 fell into a single complementation group that was mapped by genetic recombination. Two genes in this interval, *acr-17* and *acr-23*, encode predicted nicotinic acetylcholine receptor (nAChR) subunits. DNA sequencing of the corresponding regions from individual mutants revealed 27 independent mutations in *acr-23*. The ACR-23 protein belongs to a nematode-specific subfamily of nAChRs, which does not occur in mammals. Its role is the first biological function to be described for ACR-23. The *acr-23* mutants did not exhibit any overt phenotypes other than resistance and were fully susceptible to levamisole, ivermectin, benomyl, aldicarb and DMPP. Eleven resistance mutations result in truncation of the gene product and are likely null alleles that do not produce any functional protein. The finding that high-level (>1000-fold) resistance is the major phenotype resulting from loss of functional ACR-23 protein is most simply explained by hypothesizing that the substance is a direct agonist of ACR-23-containing ion channels. However, it remains possible that pathway activation results from compound interaction at another point, e.g. via inhibition of a negative regulator of ACR-23. The specificity towards *acr-23* would explain the low toxicity to organisms other than nematodes.

General pharmacology

The general safety-related pharmacological effects have been investigated in rats. There was no effect on intestinal motility and stomach weight in a charcoal propulsion test, and no changes in the Irwin screen test at the oral limit dose of 2000 mg/kg bodyweight (bw) in rats. Effects on cardiovascular and respiratory parameters were studied in the anaesthetised rat after an intraduodenal dose of 2000 mg/kg bw. Systolic, diastolic and mean blood pressure, heart rate, electrocardiograms, respiratory rate, tidal volume and minute volume (calculated) were monitored before and for up to 4.5 hours after treatment. The effects were limited to a small decrease in mean respiratory rate and minute volume but this change was considered not to be biologically significant. Furthermore, the observations in the toxicological and target species tolerance studies provided no evidence of a pharmacological effect. Since no specific signs were observed even in high single and repeated dose studies in the various species (mouse, rat, rabbit, dog, sheep), it is concluded that the compound is devoid of a relevant pharmacological activity in mammals.

Pharmacokinetics

Laboratory animal species

In rats the bioavailability based on ^{14}C-monepantel was approximately 30 % after a single oral dose of 2.5 mg/kg bw. The terminal elimination of radioactivity from plasma occurred roughly monoexponentially with half-lives between 40 and 60 hours. The oral bioavailability of parent monepantel was estimated to be 9.4 % indicating that a part of the absorbed oral dose is eliminated by first-pass metabolism. Monepantel was excreted mainly via the faeces (70 to 97 %) within 3 days. Metabolite monepantel-sulfone profiles in faeces showed mainly unchanged parent (25 % of the mean daily dose) and the metabolite (hydoxylated sulfone, 52 % of the daily dose).

After repeated daily oral administration of 10 mg/kg bw for seven days, the major part of the administered radioactivity was recovered in faeces (60 to 80 %) and some in urine (3 to 6 %). Females showed a somewhat slower metabolism/elimination than males. Total (^{14}C) residue concentrations were generally highest in the liver and fat, followed by adrenals, pancreas and ovaries. Concentrations were low in blood and muscle and intermediate in kidney. The residue levels in organs and tissues were generally higher in females than in males.

In all tissues residues were characterized as mainly parent drug and the sulfone metabolite. In addition three minor metabolite fractions and a further five very minor fractions were detected in tissues.

In dogs, no formal metabolism study has been undertaken, but pharmacokinetic data for non-radioactive monepantel after intravenous, oral and dermal administration are available. The parent compound was observed initially but depleted relatively quickly from blood. The sulfone metabolite was the dominant metabolite, appearing later and depleting rather slowly compared to in rats and sheep. The sulfone metabolite was seen to accumulate in dogs, while it did not accumulate in rats or sheep, but this accumulation was not related to the cytotoxicity seen in repeated dose studies in dogs.

In vitro studies using liver microsomes were performed to determine the intrinsic clearance of parent compound in mouse, rat, dog and human, with a view to monitoring a possible relationship between toxicological response and metabolic stability of parent compound in various species and to comparing the interspecies pattern and nature of metabolites. High intrinsic clearance values of monepantel (at 1 µmol/l) were observed in liver microsomes of rat and man whereas only moderate values were determined in liver microsomes of mouse and dog. The pattern of metabolites in incubations at 10 µmol/l monepantel was comparable between the four species. However, an additional minor metabolite (P32.5) was formed in rat and human microsomes. Data from *in vivo* studies show that this metabolite is not present in edible sheep tissues.

Toxicological studies

Single dose toxicity

The results of single oral dose studies in rats indicated low acute toxicity of monepantel. Following oral as well as dermal administration, the lethal dose was greater than the limit dose of 2000 mg/kg bw in rats. No substance-related effects were identified on respiration rate, body temperature, blood pressure or heart rate. Monepantel was considered to possess low acute toxicity.

Repeated dose toxicity

Repeated dose toxicity in rats

Three repeated dose toxicity studies have been carried out in rats. Consistent with the pharmacokinetic data, female rats were generally more sensitive than male rats.

The first study was a 4 week non-GLP study in which animals were exposed to monepantel in the diet at 0, 1000, 4000 and 12000 mg/kg feed corresponding to 0, 90, 350, or 1000 mg monepantel/kg bw/day. The compound was clinically well tolerated at all concentrations. Increased cholesterol, triglycerides and phospholipids indicating changes in lipid metabolism and increased liver weights were seen at all dose levels in females and at 4000 and 12000 mg/kg feed in males. Centrilobular hypertrophy of the liver and follicular hypertrophy of the thyroid was observed at all dose levels. No NOEL could be set.

The second rat study was a 13-week GLP study. Monepantel was administered in the diet at 0, 50, 200, 1000 or 12000 mg/kg feed corresponding to 0, 4, 15, 75 and 900 mg/kg bw/day. No clinical signs were observed and no differences in body weight were detected. The main targets were the liver and lipid metabolism. Small changes were observed in plasma glucose, phospholipids, triglycerides, bilirubin, and albumin in the highest dose groups (1000 and 12000 mg/kg feed) and mainly in females. Liver weights were increased in females at 1000 and 12000 mg/kg feed. Centrilobular hepatocellular hypertrophy was present in 30 % of females at 1000 mg/kg feed and in all females at 12000 mg/kg feed. A NOEL of 15 mg/kg bw/day (200 mg/kg feed) was determined.

The third study in rats was a 52-week GLP compliant study. Monepantel was administered in the diet at 0, 50, 200, 1000 or 12000 mg/kg feed corresponding to 0, 2.7/3.4, 10.7/14, 54/67 and 656/778 mg/kg bw/day for males/females. There were no clinical signs and no effects on food consumption or body weights that were related to treatment. In clinical chemistry, increased protein, albumin and globulin levels, and decreased glucose levels were considered possibly treatment related at 12000 mg/kg feed. Increased cholesterol, triglycerides and phospholipids were observed at 12000 mg/kg feed. Elevated liver weights were observed at 1000 and 12000 mg/kg feed. It was concluded that effects on lipid metabolism, plasma proteins and liver weight were the main effects at the high dose. There was no indication of proliferative lesions. A NOEL of 14 mg/kg bw/day (200 mg/kg feed) was established.

Repeated dose toxicity in mice

A repeated dose (GLP) toxicity study over 3 months was carried out in mice. Mice were exposed to monepantel in the feed at 0, 30, 120, 600 or 6000 mg/kg feed, corresponding to 0, 5, 18, 100 or 1000 mg/kg bw/day, respectively. No treatment-related clinical signs of toxicity and no significant differences in body weight or food consumption were observed. In clinical chemistry, changes were observed in bilirubin, cholesterol, alkaline phosphatase, aspartate transaminase and alanine transaminase at 600 and 6000 mg/kg feed and slightly increased plasma activity of ASAT in all male treated groups and in females at 120 ppm and above. Microscopic changes were observed in the liver at 600 and 6000 mg/kg feed and consisted of predominantly centrilobular fatty change. A NOAEL of 18 mg/kg bw (120 mg/kg feed) was retained.

Repeated dose toxicity in dogs

Three repeated-dose, GLP compliant toxicity studies have been carried out in dogs. In the first study animals were dosed with 0, 5000, 15000 and 40000 mg/kg feed (161/184, 566/561, 1217/1472 mg/kg bw/day males/females) for 4 weeks. Treatment was well tolerated despite some body weight loss in males in the high dose group. Increased alkaline phosphatase activities and adrenal weights at all dose levels and increased liver weights in females given 40000 mg/kg feed were not associated with histological correlates and no other parameter indicative of potential liver damage was effected. Lower thymus weights and thymus involution were noted in the high dose group. No NOEL could be established as effects were seen at all dose levels.

In the second study dogs received monepantel for 13 weeks in the feed at 0, 300, 3000, or 30000 mg/kg feed (9.9/10.7, 97/107, 963/1176 mg/kg bw/day males/females). Food consumption was not affected by treatment but a lower body weight gain was recorded in females given 30000 mg/kg feed during the treatment period. Treatment related changes in alkaline phosphatase values were noted in all groups but the biochemical parameters alanine transaminase and aspartate transaminase were not affected. In the highest dose group in females, gamma-glutamyl transpeptidase was increased. Higher liver weights were recorded at all concentrations in both sexes at the end of the treatment period. No treatment-related necropsy findings were noted. Upon microscopic examination treatment-related changes were noted in the liver (hepatocellular hypertrophy, biliary proliferation, brown pigments in Kupffer cells and hepatocytes), small intestine (dilatation of glands) and pancreas (increased apoptosis) in the various groups. An increased incidence and/or severity was seen for hepatocellular lesions at 3000 and 30000 mg/kg feed in both sexes. The bile duct proliferation, the brown pigment in hepatocytes/Kupffer cells and the increase in alkaline phosphatase activity could all be related to potential liver cholestasis. One female showed a slight hypertrophy as well as higher liver weight and increased alkaline phosphatase at 300 mg/kg feed. Findings in the pancreas and small intestine were seen in all dose groups. A NOEL could not be set as effects were seen at all dose levels.

The third study in dogs was conducted over 52 weeks. Monepantel was administered in the diet at 0, 100, 300 or 3000 mg/kg feed corresponding to 0, 3/3, 8/10 and 91/99 mg/kg bw/day for males/females. Reduced body weight gain was recorded in animals at 3000 mg/kg feed. Higher alanine transaminase (both sexes) and gamma-glutamyl transpeptidase (males only) activities, lower total protein, albumin and calcium levels and lower albumin/globulin ratios were noted at 3000 mg/kg feed. At the concentration of 300 mg/kg feed, lower albumin levels and albumin/globulin ratio were observed in females. At all feeding levels, effects on alkaline phosphatase activity and liver weights associated with hepatocellular hypertrophy indicated the liver as the main target organ. Elevated adrenal weights associated with cortical cell hypertrophy and elevated thyroid weights without a histopathological correlate were seen in the mid and high dose groups. Brown pigmentation in hepatocytes and Kupffer cells as well as increased proliferation of smooth endoplasmic reticulum membranes, dilated intestinal glands (probably related to increased turnover of goblet cells and mucosa production and secretion), minimal increase of brown pigmentation in tubular cells of kidney, and increased apoptosis of pancreas acinar cells were also observed at the lowest dose but were also seen in the control groups. Microscopic examination showed bile duct hyperplasia in the liver of both sexes at 3000 mg/kg feed. No proliferative pre-neoplastic lesions were observed. After withholding treatment effects were seen to decrease (although not to control levels at 4 weeks) indicating that the changes are reversible. While a dose related response was evident for the liver effects, particularly the increase in alkaline phosphatase activity, the overall conclusion from the statistical analyses (using analysis of variance) was that the effects were not statistically significant at the lowest dose of 3 mg/kg bw/day. Based on this, a NOAEL of 3 mg/kg bw/day was established.

Repeated daily administration of monepantel admixed to the diet was well tolerated in rats, mice and dogs even at high concentrations. The main target organ was the liver. The NOEL in the rat was 14 mg/kg bw/day and the NOAEL in the mouse was 18 mg/kg bw/day. The dog was established as the most sensitive species where an increase in alkaline phosphatase activity and elevated liver weights associated with hepatocellular hypertrophy were noted in the 52 week study. Furthermore elevated adrenal weights associated with cortical cell hypertrophy and elevated thyroid weights without a histopathological correlate were seen in the mid and high dose groups. While a dose related response

was evident for the liver effects, particularly the increase in alkaline phosphatase activity, the statistical analyses (using analysis of variance) revealed that the effects were not significant ($p<0.05$) at the lowest dose of 3 mg/kg bw/day.

Tolerance in the target species of animal

Adult sheep

A target animal safety study was conducted in sheep at 50, 75, 100 and 125 mg/kg bw (33 times the maximum recommended dose of 3.75 mg/kg bw). At 125 mg/kg bw there was a transient decrease of appetite, slight increases in fluoride oxalate glucose, serum glucose and urea concentrations, a slight trend towards increased alanine aminotransferase concentrations, and slightly decreased haemoglobin concentrations. At 100 mg/kg bw, only the slightly decreased haemoglobin concentration could be considered treatment-related. It was concluded that the sheep tolerated single dose levels of up to 33 times the maximum therapeutic dose very well, without toxicologically significant changes in any of the observed parameters.

Tolerability in Merino and Suffolk lambs – single dose

This study was designed to investigate the tolerability of the final formulation (A-20072 B) at 10x (37.5 mg/kg bw) the maximum recommended dose in 2–4 week old Merino and Suffolk lambs. For each breed, males and females were treated with the product or with saline (control). A single dose was administered. Subsequently animals were observed every hour on the day of treatment and twice daily thereafter. Veterinary examinations (days -7, -4, 0, 7, 14 and 21), collection of blood specimens (days -7, 0, 7, 14, 21) and necropsy examination and histopathological harvesting of tissues (day 22+) also was performed. The ewes suckled their lambs on pasture and the flock was managed in this environment prior to and during the study. Apart from 2 study animals (and 1 replacement animal), all lambs survived and thrived until sacrifice. There was a clear clinical and pathological explanation for the deaths of the 3 animals, namely that inadvertent administration of the test item into the respiratory tract rather than into the gastrointestinal tract resulted in aspiration pneumonia and death. There were no other treatment-related clinical veterinary observations found in all other test item or saline treated lambs. No differences in haematological, coagulation and clinical chemistry variables between test item and control item treated lambs were found. The lambs grew at a normal rate and there were no differences in body weight between test item and control item treated lambs. Finally, no significant test item-related macroscopic or microscopic changes were found apart from aspiration pneumonia discussed above.

Tolerability in lambs – repeated dose

This study was designed to evaluate the tolerability and identify adverse effects of the formulation A-20072 B when administered orally every 3 weeks, on eight occasions, to 12–15 week old Merino lambs. Dose levels in terms of monepantel corresponded to 1x (3.75 mg/kg bw), 3x (11.25 mg/kg bw) and 5x (18.75 mg/kg bw) of the maximum recommended dose. The study commenced shortly after lambs were weaned. Animals were observed closely during and immediately after the treatment period followed by observations every second hour for 10 hours. Thereafter, lambs were inspected twice daily. Veterinary examinations, collection of blood specimens for clinical pathology and analysis of blood concentrations of monepantel and monepantel sulfone (main metabolite), collection of faeces for faecal scoring and necropsy examination and histopathology were performed.

All lambs survived and thrived to the end of the study. No treatment-related adverse events occurred. There were no significant clinical observations found in test item or saline treated control lambs throughout the study. There was no difference in feed consumption and water consumption between the treated and control groups. Veterinary examinations of all lambs prior to and during the study were normal for all systems examined. There was no difference between the body weights of treated and control animals at any time point. The consistency and colour of faeces collected from all lambs, regardless of treatment group was normal for the duration of the study. No differences in haematological, coagulation and clinical chemistry variables between test item and control item treated lambs were found. Finally, no significant macroscopic or microscopic changes were found in

the test item treated lambs compared to saline treated lambs. 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 of the treated versus control lambs.

Oral administration of 10x the maximum recommended dose of monepantel was systemically well tolerated in young, growing Merino and Suffolk lambs. Likewise no adverse effects were identified and no differences in response to treatment were noted between groups of Merino lambs given the formulation at 1x (3.75 mg/kg bw), 3x (11.25 mg/kg bw) and 5x (18.75 mg/kg bw) every 3 weeks, on eight occasions. The product is well tolerated.

Reproductive toxicity, including teratogenicity

Studies on the effects on reproduction

In a GLP compliant study monepantel was administered orally to 2 successive generations (F0 and F1) of male and female rats by admixture in the diet at 0, 200, 1500, and 12000 mg/kg feed (10/32, 82/245, and 650/2000 mg/kg bw/day in males/females). There was no mortality and no treatment related clinical signs. Food consumption and body weights were similar in all groups. Mating, fertility, conception and gestation were all 100 %. Precoital time and gestation length were not affected. Implantations, post implantation loss, viability index, and weaning index were all unaffected. Sperm analysis did not reveal any difference between control and dosed males. Increased adrenal weights and relative liver weights were observed at 1500 and 12000 mg/kg feed in P and F_1 females. Liver weights were also increased at 12000 mg/kg feed in F_1 and F_2 pups. No treatment-related changes were noted in macropathology. Histopathological evaluation revealed centrilobular hepatocellular hypertrophy and cortical cell hypertrophy of the zona glomerulosa in the adrenal glands of P and F_1 females at 1500 and 12000 mg/kg feed. A NOEL of 200 mg/kg feed corresponding to 32 mg/kg bw/day was established.

Embryotoxicity/foetotoxicity, including teratogenicity

In a GLP compliant oral gavage embryo/foetal development study in rats, monepantel administered at doses of 0, 100, 300 and 1000 mg/kg bw/day (during gestation day 6 through 20) caused no adverse effect on embryonal and foetal development. NOELs for maternal and foetal toxicity and for teratogenicity were 1000 mg/kg bw/day.

Similarly, in a GLP compliant oral gavage embryo/foetal development study performed in rabbits administered doses of 0, 100, 300 and 1000 mg/kg bw/day (during gestation day 6 through 27), no adverse effect on embryonal and foetal development was observed. NOELs for maternal and foetal toxicity were 1000 mg/kg bw/day. Monepantel did not show any teratogenic potential under the conditions of the study.

Mutagenicity

Monepantel was tested in a comprehensive series of mutagenicity test systems with studies performed under GLP conditions. In the standard test packet, monepantel did not provide any evidence of mutagenic activity.

Carcinogenicity

Two GLP compliant carcinogenicity studies have been conducted, one in rats and one in mice. In rats monepantel was administered in the diet at 0, 100, 1000 or 12000 mg/kg feed corresponding to 0, 4.6/5.6, 47/57 and 578/707 mg/kg bw/day in males/females. No specific clinical signs could be observed and linked with the treatment. A consistently slightly lower mean body weight development in females fed with 12000 mg/kg was considered to be test item-related but non-adverse because of the low magnitude of the change. Slightly increased liver, kidney and heart weights were recorded in females fed with 1000 or 12000 mg/kg. In the absence of any correlating microscopic findings, these effects were considered to be possibly test item-related but non-adverse. The incidence, onset and location of palpable nodules/masses did not distinguish test item-treated rats from their respective

controls. Similarity, the incidence of histopathological lesions did not indicate any effect of treatment. Monepantel was not considered to be carcinogenic in rats.

In mice, an 18-month carcinogenicity study was conducted. Monepantel was administered in the diet at 0, 10, 30, 120 or 500 mg/kg feed corresponding to 0, 1.5, 5, 20 or 69/92 (males/females) mg/kg bw/day. No specific clinical signs could be observed and linked with the treatment. A statistically significant increase in absolute and relative liver weights was noted in females at 120 and 500 ppm. Microscopically, increased incidences and severities of fatty liver were noted in males and females at 120 and 500 ppm. Due to the mostly macrovesicular appearance of fatty liver, this alteration was considered to be indicative of increased lipid metabolism or decreased availability of transporter mechanisms. No further indicator of adverse liver injury was recorded and hence, this lesion was deemed to be an adaptive, metabolic response rather than an adverse effect. In addition, indicators of microvesicular steatosis were not seen. There was no indication of an oncogenic potential of monepantel in this study.

Monepantel has no carcinogenic potential in mice and rats.

Studies of other effects

Special studies

Studies of other effects including immunotoxicity and neurotoxicity

A study was performed on skin sensitisation potential using Local Lymph Node Assay. No cutaneous reaction or lymphoproliferation were noted at any tested concentration. Concerning acute dermal irritation in rabbits no effects were observed. With acute eye irritation in rabbits a slight redness of the conjunctiva was observed on day 1 leading to the conclusion that the product is slightly irritant to the eyes.

Monepantel was not irritating in an acute dermal irritation test in rabbits. In the local lymph node assay monepantel did not induce delayed contact hypersensitivity. An acute eye irritation test in rabbits showed that monepantel is a slight irritant. As the scores of the reported eye irritation were low and the effects were only present until 24 hrs after removal of the compound, we do not consider it necessary to propose a specific warning for eye irritation. Moreover, in contrast to the eye irritation test in which rabbits were exposed to a single dose of 100 mg monepantel, monepantel in ZOLVIX is diluted in a formulation of 25 mg/ml, meaning that a total volume of 4 ml ZOLVIX should come into contact with the eyes to reach the same dose. This is highly unlikely.

Studies on metabolites, impurities, other substances and formulation

Based on structure-activity modelling the potential toxicological properties of the impurity N-[2-(5-cyano-2-trifluormethyl-phenyloxy)-1-(S)-1-cyano-1-methyl-ethyl]-4-chloro-benzoic amide, specified at ≤0.5 %, did not raise a specific toxicological concern in addition to that relevant to the parent compound.

Mutagenicity studies with the sulfone metabolite did not show any mutagenic potential, as reported in the *Mutagenicity* section, above.

User Safety

Inherent Toxicity

The formulated product is a solution containing 2.5 % active ingredient. It is administered with a drenching gun directly into the oral cavity of sheep. The equipment can be considered a closed system since the drenching gun is connected directly to the product container via tubing. Contamination of the user is possible by accidental spillage, misadministration, if the equipment is leaking, or during cleaning. Acute oral and dermal toxicity studies in rats show that the formulated product is devoid of a hazard potential and does not require classification according to the Council Directive 67/548/EEC

(and subsequent adaptations). As regards skin and eye irritation studies any observed irritation was below the threshold criteria for classification. Although the formulation appeared positive at the high concentration in the mouse local lymph node assay, this was related to the irritant potential and overall the study was interpreted as an inconclusive. In view of a clearly negative result for the active substance and absence of excipients with sensitizing properties, the formulation is considered to be devoid of a relevant skin sensitizing potential.

Exposure of the user

Various worst case scenarios were considered in the Operator Safety Assessment. It is concluded that the product containing monepantel at the concentration of 25mg/ml presents no acute hazard to the users. It is unlikely that a toxic dose could be ingested accidentally, based on the toxicity of the active ingredient and the formulation (oral LD50>2000 mg/kg bw for both). The physico-chemical properties of the active ingredient do not indicate a particular hazard. The extent of the expected maximum one day systemic exposure when treating a very large flock of sheep (2000) was compared to the lowest NOAEL (10 mg/kg bw) of the sub-chronic repeat-dose oral toxicity studies. The dermal operator exposure to the active ingredient was calculated to be 0.57 mg/kg bw. Assuming a worst case dermal absorption of 4.5 %, the systemic exposure would be 0.026 mg/kg bw. This exposure is about 100 times lower than the lowest NOAEL of the 52 week repeat-dose oral toxicity studies in dogs (3 mg/kg bw). The safety margin of 100 is considered sufficient.

Conclusion including the risk management proposals

It is concluded that no unacceptable health risk to operators is associated with the use of monepantel in sheep. The only warning considered necessary is that the product be kept out of reach of children, and it is recommended to wear impermeable gloves while handling the product.

Monepantel formulated product does not possess risks to the user. It has to be noted that the safety margin mentioned is based on toxicity studies with repeated daily exposure while the operators applying the product will not be exposed daily for an extended period of time. However, based on the toxicity studies and the proposed special precautions for use, and considering the worst case exposure scenario, it is agreed that ZOLVIX 2.5% oral solution for sheep does not pose a risk to the user.

Environmental Risk Assessment

Phase I Assessment

It has been considered unnecessary to conduct a Phase I assessment, as it could be justified to guide the product to a Phase II assessment in any case due to its endoparasiticidal use in pasture animals.

Phase II Assessment

The relevant exposure scenarios is identified on the basis that sheep and lambs are almost exclusively raised on pasture wherefore the intensive reared animal scenario can be excluded in the risk assessment. On grassland, the soil and dung organisms may be exposed directly as a result of excretion whereas adjacent fresh and ground water systems may be exposed indirectly via run off and leaching or theoretically directly via urination or defecation directly in the water body. Risk to all relevant compartments therefore needs to be evaluated.

Pattern of use and metabolism in target species

After oral administration, monepantel is readily absorbed and oxidised to a sulfone metabolite. Peak blood concentrations are reached within one day. Hereafter blood concentrations decrease with a half life of about five days. Excretion is mainly via the faeces but also to a lesser degree via the urine.

The ADME study showed that the faecal metabolites were structurally close to the parent drug, whereas urinary metabolites corresponded to the parent molecule cleaved into two halves.

Monepantel- sulfone was the most prominent faecal metabolite followed by the parent molecule (particularly during the first days) and another metabolite named F24.

Chemical-physical properties

The physical-chemical properties of the parent drug have already been presented. The substance has relative low water solubility and moderate log K_{ow}, and is non-photodegradable and non-volatile.

Monepantel may be considered as potentially bioaccumulative. ADME studies with rats, sheep and lambs indicate however a low potential for bioaccumulation. Monepantel is not carcinogenic, mutagenic or toxic to reproduction. There is no evidence of high chronic toxicity. Based on the acute aquatic toxicity data, monepantel does not meet the screening criteria for Toxicity. However the PBT dataset is incomplete since a BCF study in fish is not available, nor are chronic toxicity studies with aquatic organisms available. Read across with other substances is not possible, since this is the first compound of a newly developed class. CVMP concludes that monepantel is **P**ersistent and potentially **B**ioaccumulative. However the likelihood of food chain magnification or significant bioaccumulation in aquatic species appears to be very low.

Risk – Surface Water

Fresh water organisms may be exposed VMPs and their degradation products via substances leaching from the soil through surface run-off or leaching or through direct excretion by animals in the water body. In the case of sheep, the latter is generally omitted as it is believed to be very unlikely that these will enter water bodies. No risk to aquatic species has been identified as a result of normal use. The same conclusion would be true even if the scenario of direct excretion would be included.

Risk - Groundwater

The predicted ground water concentration does not exceed the limit of 0.1 $\mu g\ L^{-1}$. Therefore the risk to groundwater is considered negligible.

Risk – Soil

The substance is likely to reach the terrestrial environment through excretion from medicated animals. As a consequence of its relatively high persistence, it may accumulate in soil. According to the calculations no unacceptable risk to soil organisms has been identified.

Risk – Dung organisms

Apparent risk has been identified for dung insects with the greatest risk quotient of 2.7 for dung flies exposed to the parent based on a 30% dung dry weight[1] PEC of 40 mg/kg and an estimated PNEC of >15mg/kg. This PNEC is derived from the NOEC of >1000 mg/kg and a safety factor of 100: Since the dung fly study was designed as a limit test, an EC_{50} was not determined. It is considered that based on the above the risk quotients would exceed 1 on the first and minimally on the second day following the treatment. Thus the dung concentrations are expected to reflect the short, sharp peak of excretion of monepantel and its sulfone metabolite immediately after dosing. Dung arthropod fauna will not be at risk for the remaining of the treatment-free period.

It is considered that based on the above the risk quotients would exceed 1 during the first 3 to 4 days following the treatment. As the risk was present for a relatively short period and at a low level (dung insects are expected to be present in dung droppings of sheep previously at pasture which serve as a reservoir for insects to colonise droppings of treated animals within a few days) no risk management measures are considered necessary.

Risk of metabolites

The ADME study (see residues section) showed that the faecal metabolites were structurally close to the parent drug, whereas urinary metabolites corresponded to the parent molecule cleaved into two halves.

A Phase II assessment of the environmental risk of the substance and its major metabolites has been conducted according to the VICH Guideline GL 38 (CVMP/VICH/90/03-Final) and the CVMP Guideline in support of VICH GL 6 and GL 38 (EMEA/CVMP/ERA/418282/2005-corr). The provided data fulfils the requirements specified in those documents. The provided tests have been conducted according to international standard guidelines and under the compliance of GLP, and test results are generally of a quality that enables a full and complete assessment. Risk to ground water, fresh water organisms or soil organisms has not been identified. A risk to dung fauna was identified: RQ values were above 1 for three, probably four days.

The target animals are raised on pasture and the product is an endoparasiticide. Therefore, a Phase II environmental risk assessment was considered necessary. In accordance with guideline requirements the following data on physico-chemical properties, fate and effects of monepantel were provided.

Physical-chemical properties and fate		
Study type	**Test protocol**	**Results**
Water solubility	OECD 105	0.08 g/l at 25°C
pKa		n/a
Dissociation constants in water	OECD 112	n/a
UV-Visible Absorption Spectrum	OECD 101	n/a
Melting Point/Melting Range	OECD 102	142-159°C
Vapour Pressure	OECD 104	2.8 x 10^{-9} Pa at 25°C
n-Octanol/Water Partition Coefficient	OECD 107	4.7 (log K_{ow}, QSAR estimate)
Soil Adsorption/Desorption	OECD 106	Koc: 6907-8880 dm^3/kg Kd: 81-295dm^3/kg
Soil Biodegradation	OECD 307	DT_{50} : 38 – 146 days

Phase II, Tier A Effect studies				
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**
Algae, Growth Inhibition Test	OECD 201	EC50	>100,000	µg/l
Daphnia sp. immobilization	OECD 202	EC50	>100,000	µg/l
Fish, acute toxicity	OECD 203	LC50	>100,000	µg/l
Nitrogen Transformation	OECD 216	< 25% effect	300	µg/kg
Terrestrial plants	OECD 208	EC50	>100,000	µg/kg
Earthworm subacute/reproduction	OECD 220	NOEC	2400	µg/kg
Dung fly larvae	OECD 228	EC50	>1,000,000 1,035,000*	µg/kg
Dung beetle larvae	OECD draft	EC50	1,991,000 940,000*	µg/kg

*Values for metabolite monepantel sulfone

Based on the data provided ZOLVIX is not expected to pose a risk to the environment when used according to the SPC. The active principle monepantel is not expected to leach to groundwater.

RESIDUE DOCUMENTATION

Precise identification of the product concerned by the application

Formulation used in the residue studies (related to the formulation of the final product)

Nature and position of the label, the activity and the radio purity of the labelled substances in the radio-tracer studies

For the studies, the active ingredient was labeled at either of 2 different positions with carbon-14, referred to as "label 2" or "cyano" and "label 3" or "amide". In one instance, a mixed label test material was used, and it consisted of equal parts "label 2" and "label 3", referred to "label 2+3". The radio-purity of these substances was 99% or greater.

Elimination of (^{14}C) parent compound (S-enantiomer biologically active) in rats occurred almost exclusively after biotransformation. Based on LC-MS analysis and comparison with reference compounds, the structures of metabolites are:

Residue studies

Pharmacokinetics

Sheep

Two studies investigating absorption, distribution, metabolism and elimination (ADME) were conducted in sheep. In a pilot study sheep received a single oral dose of 5 mg/kg bw ^{14}C-monepantel. Excreta were collected quantitatively during 12 days and blood and tissue were collected. Due to inhomogeneity of the test formulation, the doses administered were less than anticipated, and could only be estimated. Consequently, accurate figures for excretion and balance are not possible. However data indicate that 17 or 39% of the radioactivity were eliminated within 12 days via urine and 71 or 53% via faeces. The retained dose was distributed mainly in the muscle (5-6%) and fat (1-2%). The sulfone of the parent substance was the predominant molecule in blood and tissues.

A second ADME study in sheep to investigate the residue depletion as well as absorption, distribution, metabolism and excretion of (^{14}C)-monepantel after single oral administration at 5 mg/kg bw to sheep was also reported in detail. Sheep were orally dosed at 5.0 mg/kg bw and blood, excreta, wool and tissues were collected. The radioactive substances were dissolved and sheep were dosed with either label 2, label 3 or an equimolar mixture of each labeled substance. Collected samples were analysed for total radioactivity, metabolite profiles and by HPLC-UV for the parent drug and metabolite (monepantel-sulfone).

Data show that radioactivity is predominantly excreted through the faeces with a significant contribution from urinary elimination. Faecal excretion is high in the first 3 days (about 30%), but then slows down, with about 2-3 weeks required for 90% elimination. Blood and plasma profiles, obtained from 4 sheep dosed with label 2 substance indicate a very slow elimination of total radioactivity from the systemic circulation. Highest residues in edible tissues are found in the fat, with slightly higher residues in rendered pure fat compared with fat tissue ("composite"). Liver is also an organ of accumulation. Muscle has the lowest residues.

The collected tissue and blood samples were analysed by HPLC with UV detection for the parent drug and metabolite (monepantel-sulfone). Blood levels were consistent with data observed in PK studies and plasma results confirm the blood-plasma distribution ratio of about 1, for both parent and sulfone. The approximate metabolite proportions were 200:100:30:20:1:1 in fat tissue : liver : kidney : muscle : blood : plasma (mean of proportions for individual sheep). Stability data suggest that metabolites in tissues are stable. Elimination is predominantly via faeces, with significant contribution from urine. Bile excretion contributes to total faecal elimination. A tiny fraction of the drug is excreted with wool. The proposed pathway is similar to that proposed for rats with one exception. In the rat more minor

polar metabolites were observed, most likely because the rats were sacrificed at earlier times and repeatedly dosed (or simply because rats are more metabolically active).

This pivotal study was well conducted with ample animal numbers. The chromatographic and spectral data support the proposed metabolites.

A GLP study was performed to examine the pharmacokinetics of the parent compound and the metabolite monepantel-sulfone, involving the final oral formulation (1, 3 and 10 mg/kg bw), and with intravenous administration of the parent compound and the metabolite monepantel-sulfone. No adverse events were observed after oral administration, up to 4 times the nominal dose rate, but after the intravenous dose, some animals suffered from transient "bloody' urine, attributed to hemolysis caused by DMSO, an excipient in the intravenous solution. Collected blood and faecal samples were analysed for the parent compound and the metabolite monepantel-sulfone. The calculated PK parameters were analysed. Absolute bioavailabilities of the parent and metabolite monepantel-sulfone are around 31% and 94% after an oral dose of 1 mg/kg bw of the parent compound. The difference between the two bioavailabilities is likely caused by a first-pass effect.

Dose-linearity for the parent compound appears to hold for oral administrations of 1 to 10 mg/kg bw, but for the metabolite monepantel-sulfone, dose-linearity is only observed up to the 3 mg/kg bw dose. At 10 mg/kg bw, proportionately less metabolite is formed (the AUC ratio for metabolite/parent decreases from ~16 to 10 at the highest dose), suggesting that the liver enzymes are saturated at the higher dose. Faecal clearances are ~0.05 and ~0.08 l/kg per hr for the parent compound and the metabolite monepantel-sulfone respectively, after intravenous administration of the respective drugs. The calculated faecal clearance of the parent after oral administration is 1.1 l/kg per hr; a significant proportion is excreted with the faeces without being absorbed. A rather small fraction of absorbed parent drug (3.7 %) is excreted via faeces; the remaining drug is mainly converted to metabolite monepantel-sulfone, of which 27% is excreted via faeces and the remaining 73 % are further metabolized.

A study was also conducted to examine the bioequivalence between the final formulation of monepantel product and the formulation used in the pivotal ADME study. Merino lambs, infected with 5 roundworm species, were orally dosed at 2.5 mg/kg bw with either formulation TG1778/30 or A-20072B, and blood samples were collected. Samples were analysed for the parent and sulfone. PK parameters (not corrected for dose rate) were calculated and compared for bioequivalence. Statistical analyses indicated the 2 formulations were equivalent in the range of 0.8-1.25.

The pharmacokinetic studies were well conducted. Dose-linearity for monepantel appears to hold for oral administrations of 1 to 10 mg/kg bw, but for the metabolite monepantel-sulfone, dose-linearity is only observed up to the 3 mg/kg bw dose. At 10 mg/kg bw, proportionately less of the metabolite monepantel-sulfone is formed.

Protein binding

A GLP study was conducted to investigate the binding of (^{14}C) monepantel (label 2) to proteins in rat, dog, sheep and bovine plasma, using equilibrium dialysis against ultrafiltrated (protein free) plasma. Initial experiments confirmed the stability of monepantel in rat plasma and 30 h were required to reach equilibrium. The protein binding was >99 % for rat and dog plasma, and 98.4 % and 97.2 % for bovine and sheep plasma respectively. This study was well conducted, using appropriate concentrations.

Depletion of residues

Three depletion studies (2 in lambs and 1 in sheep) with single administration of unlabelled monepantel have been conducted. In the first study, lambs were slaughtered at 7, 18, 29 and 40 days and in the second study at 7, 19, 29, 40, 70 and 77 days after administration. In the final study sheep were slaughtered at 7, 18, 29, 35, 70, 120 and 127 days after administration. In all studies residues were highest in fat followed by liver, kidney and muscle. The unlabelled analytical method used in

these studies was the proposed regulatory method for the sulfone metabolite with a limit of quantification of 50 µg/kg. Additional solid phase extraction clean-up was used to lower the limit of quantification to 10 µg/kg, and hence increase the number of quantifiable values for statistical purposes

MRLs

Based on a NOAEL of 3 mg/kg bw, derived from the 52 week repeated toxicity study in dog and considering a safety factor of 100, an ADI of 0.03 mg/kg bw or 1.8 mg/60 kg person has been established previously: see EPMAR for monepantel EMEA/CVMP/165324/2008-corr http://www.emea.europa.eu/pdfs/vet/mrls/16532408en.pdf.

The sulfone metabolite has previously been selected as an appropriate marker for residues as it represents a large and relatively constant fraction of total residues in all tissues (90% in muscle, 60% in other tissues).

Monepantel is included in Annex I of Council Regulation (EEC) No 2377/90 for ovine species in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Monepantel	Monepantel-sulfone	Ovine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption

Using the fraction of total residues represented by the proposed MRLs and the standard consumption factors the theoretical dietary intake comprises 84 % of the ADI.

Withdrawal periods

For all the tissues the MRLs are somewhat higher than the highest measured residue on day 7, found in sheep treated at the highest recommended rate (3.75 mg/kg bw). The MRLs are also higher than the arithmetic mean plus 3xSD at day 7. As the first sampling point is 7 days the residue data did not lend themselves to the statistical approach for determining a withdrawal time. Total (^{14}C) residues of monepantel-sulfone observed at day 7 in the pivotal sheep ADME study confirm that all tissue concentrations at day 7 are well below the MRLs (muscle: 450 µg/kg, fat: 5800 (pure fat 7300) µg/kg, liver 2700 µg/kg and kidney 810 µg/kg; these data were generated with sheep dosed at 5 mg/kg bw, which is 33% higher than the proposed maximum dose rate.

It was considered that the withdrawal period could be set at 7 days.

Analytical method(s)

Description

A validated HPLC method with UV detection for determination of the sulfone metabolite of monepantel in tissues (fat, liver, kidney and muscle) of sheep is available according to the current requirements of Volume 8 of The Rules Governing Medicinal Products in the European Union. The limits of quantification for ovine tissues were 51 µg/kg for fat, 56 µg/kg for liver, 13 µg/kg for kidney and 15 µg/kg for muscle.

Conclusion on the Residue Part

At the first sampling point at 7 days after administration the marker residue (monepantel sulfone) is below the MRL in all tissues. It is agreed that the withdrawal period can be set at 7 days.

4. CLINICAL ASSESSMENT (EFFICACY)

PRECLINICAL STUDIES

Dose Determination Studies

Dose Determination Study against Adult Nematodes *C. ovina, C. curticei, H. contortus, N. spathiger, T. circumcinta, T. axei and T. colubriformis* in sheep

This was a parallel-group design blinded randomised controlled dose determination with induced infection and worm counts. The experimental unit was the individual sheep. Results involved the geometric worm and egg count means of untreated and treated groups, the respective reduction and the related Mann Whitney p-value (p) versus the untreated control. It was shown that all infections were statistically adequate. All worm and strongyle egg counts were significantly lower in treated sheep but for *Chabertia ovina* at 1.25 mg/kg bw. All reductions were ≥ 90% but for *Chabertia ovina* at 1.25 mg/kg bw. The minimum effective dose rate was 2.5 mg/kg bw in this study. Efficacy against benzimidazole resistant nematodes was demonstrated. Nematode infections were made intraruminally and a few sheep had tissue reactions at the site of injection, other than this there were no adverse events.

The conclusion was that the dose 2.5 mg/kg bw was highly effective against all nematode species with efficacies over 99.0%, except for *Chabertia ovina* (94.0%). The overall efficacy of the dose 2.5 mg was 99.0% based on worm count reduction. The study determined 2.5 mg of parent compound/kg bodyweight as the effective dose for treatment of adult gastro-intestinal nematodes in sheep.

Five pharmacodynamic and 9 pharmacokinetic/residue studies were submitted.

Dose confirmation Studies

Dose confirmation study against L4 of gastro-intestinal nematodes (*C. ovina, C. curticei, H. contortus, N. spathiger, T. circumcinta, T. axei and T. vitrinus*) in sheep

This was a blinded randomised controlled dose determination with induced infection and worm counts. The experimental unit was the individual sheep. Results were analysed by the geometric worm and egg count means of untreated and treated group, the respective reduction and the Mann Whitney p-value (p). It was shown that all infections were statistically adequate. All worm and egg counts were statistically significantly lower in treated sheep. All reductions were ≥ 90%. The efficacy against 4th larvae of *Haemonchus contortus, Teladorsagia circumcinta, Trichostrongylus axei, T. vitrinus, Cooperia curticei, Nematodirus battus, N. spathiger* and *Chabertia ovina* was confirmed. Efficacy against benzimidazole resistant nematodes was demonstrated.

Adequate documentation for efficacy was provided for the above mentioned species. A total of 16 dose confirmation studies were carried out, according to a similar design. Variations in reduction of worm counts as well as faecal egg counts (FECs) were observed. Such variation can be due to differences in nematode susceptibility and/or differences in exposure of nematodes to active substance in the different parts of the GI-tract (e.g. exposure of blood feeding *Haemonchus contortus* to active substance will be different from that of *Chabertia ovina*. Additionaly, not all nematode species are equally relevant from a clinical point of view.

Tolerance in the target species of animal/ Resistance/ Drench ability in comparison with other commercial anthelmintic formulations

This study was to assess the drench ability of a solution formulation using two common makes of drenching gun and to compare with two commercial drench formulations, and studied ease of pumping the formulation through a gun, differences in the force required at various temperatures and the effect or tubing caused by the formulation over time. It was shown that the drench ability of the investigational veterinary product was excellent and minimal damage, as defined in this study,

occurred to either of the guns tested with this formulation. The investigational veterinary product performed better than the commercial formulations at each of the temperatures with both guns. It is noted that the administered volume of ZOLVIX is relatively small (1 ml/10 kg bw); as can be seen from the data, volumes of other products can be about twice that of ZOLVIX. Therefore accuracy of drenching and drencheability of the product are important.

Conclusion on the Preclinical Part

CLINICAL STUDIES

Laboratory trials

Field trials

Field study to investigate the efficacy and safety as an oral anthelmintic drench administered at a minimum of 2.5 mg per kg bodyweight for the treatment of gastrointestinal nematodes in sheep

This was a multicentered, blinded, randomised controlled field study. Efficacy was defined as statistically significant egg reduction of ≥ 90%. Faecal consistency was scored from hard pelleted (0) to watery (5) and percentages of pelleted versus non-pelleted faeces in each group were compared. Post treatment egg counts were compared to the untreated controls (Mann-Whitney Test) and to the pre-treatment egg counts (Wilcoxon test). Results were analysed with % egg count reductions at various sites compared to controls or to Day 0, Mann-Whitney (MW) or Wilcoxon (W) p-value and nematode genus present at treatment. Results for faecal consistency on day 0 and day 7 as measured by % of pelleted and not pelleted faecal samples were provided. On day 0 faeces of sheep to be treated were statistically significant softer but after treatment significantly more pelleted than the faeces of untreated sheep.

There was a total of 22 adverse events, 17 in treated and 2 in untreated sheep in the blinded efficacy phase with no statistical significant difference between groups. There were 2 cases of pharyngeal and subglossal oedema, pyrexia and upper tract congestion on days 1 and 9. One sheep was found dead on day 22 with penetrated pharynx. These cases were probably treatment related drench gun injuries and therefore administration related rather than product related. It is agreed that this field study showed good efficacy for treatment of sheep gastrointestinal nematodes.

A total of 4 field studies have been carried out, on specifically addressing productivity after anthelmintic treatment. Field study efficacy was based on faecal egg counts only. Larval culturing was carried out and indicated some variation in effect on *Chabertia ovina, O. venulosum, Teladorsagia spp* and *Trichostrongylus spp.* between trial locations. The relevance of faecal consistency as an indication for worm burden or efficacy should not be overestimated.

Clinical field study to evaluate the efficacy and safety when administered to sheep, in comparison with registered anthelmintics

This was a multicentered blinded randomised controlled field study of efficacy and safety. Naturally infected (with gastro-intestinal roundworms) sheep grazing at pasture were used. The target species for which efficacy data was sought were *Teladorsagia (Ostertagia*) spp., *Haemonchus contortus*, *Trichostrongylus spp., Cooperia spp., Nematodirus spp., Oesophagostomum spp*. and/or *Chabertia ovina*. Infections varied between sites (total number of sites was 18) and were identified through coproculture or in the case of *Nematodirus spp*. by faecal worm egg count. Some adverse events were recorded in the treated group (coughing immediately after administration) but this was not considered related to the product rather to the administration procedure. Other adverse events were too late for T_{max} ≤24 h therefore not considered related to the product. The efficacy when used under field conditions was confirmed as highly effective against mixed-genus natural field infections of all the major gastro-intestinal nematodes.

At 7 days (+/- 1 day) post-treatment, the efficacy was generally >98%. The poorest result (95.9%) occurred at site 13, but the Applicant noted that there were some probable errors in labelling/processing of faecal samples and if the suspected data were excluded efficacy improved to 100%. At 14 days (+/- 1 day) post-treatment, the efficacy was generally close to or >99%. The worst results was documented at site 6 (97.3%), which could be improved to 98.3% on the basis of suspected incorrect data. At 21 days (+/- 1 day) post-treatment, efficacy started to become a little variable but was still consistently >97%. The cause of the variation was explained by the Applicant by fresh incoming larvae that matured and became reproductively active and/or adults that had matured from larval stages that survived the initial treatment. There were 4 sites with an efficacy <97% at day 21. Two of these increased to >98% on the basis of suspected errors in sample collection or laboratory processing. An overview of the results from each of the 18 sites was presented.

It is agreed that the efficacy of the product was confirmed as high when used under field conditions. As indicated in the World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline >98% is regarded as highly effective, and this was the case even if the Applicant thought that some errors had been made in labelling sample jars on-farm or in the laboratory from some sites. When data were corrected according to such errors the efficacy was always better than when data were not corrected. In several of the involved sites the efficacy tails off from week three post-treatment. This fact indicates that sheep are reinfected from the environment therefore it seems important to have a plan for grass pen rotation combined with the use of such anthelmintics. Reinfection 3 weeks post treatment can be avoided by moving animals to clean pastures. However, from the pharmacokinetic data it can be concluded that the major metabolite of monepantel monepantel-sulfone can be considered as both being effective and persistent.

Conclusion on the Clinical Part

The efficacy of the product, when used under field use conditions has been confirmed as exceptionally high and meeting various international regulatory standards. The results confirm those obtained in various dose confirmation studies and an extensive field testing programme.

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At 21 days (+/- 1 day) post-treatment, efficacy started to become a little variable but was still consistently >97%. The cause of the variation could be fresh incoming larvae that had matured and become reproductively active and/or adults that had matured from larval forms that survived initial treatment. There were four sites with an efficacy <97% at day 21. Two of these sites increase to >98% on the basis of suspected errors in sample collection or laboratory processing.

All of the major gastro-intestinal nematode genera were represented at various frequencies and incidences in this study.

In conclusion, the product when used under field use conditions at a minimum dose rate of 2.5 mg/kg bw was highly effective against mixed-genus natural field infections of all the major gastro-intestinal nematodes including *Haemonchus, Teladorsagia, Trichostrongylus, Cooperia, Nematodirus, Chabertia and Oesophagostomum*. This included efficacy against strains resistant to the currently available broad-spectrum anthelmintics.

5. BENEFIT RISK ASSESSMENT

ZOLVIX oral solution is a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes. The active substance is monepantel which is an anthelmintic belonging to the amino-acetonitrile derivative (AAD) class of molecules. Monepantel acts on the nematode specific nicotinic acetylcholine receptor sub-unit Hco-MPTL-1. This is the first biological function to be described for the Hco-MPTL-1 receptor and therefore monepantel is effective against nematodes resistant to other anthelmintic classes. The application was submitted as a full application for a veterinary medicinal product containing this new active substance.

ZOLVIX oral solution is a broad spectrum anthelmintic and the spectrum of activity includes fourth larvae and adults of: *Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcate, Teladorsagia davtiani, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus vitrinus, Cooperia curticei, Cooperia oncophora, Nematodirus battus, Nematodirus filicollis, Nematodirus spathiger, Chabertia ovina, Oesophagostomum venulosum.*

The benefit of the product is a high efficacy to all major gastro-intestinal nematodes in sheep. An additional benefit is that the active ingredient is of a new class, and to be used in a therapeutic area where resistance to substances is common. However, the efficacy has not been established in sheep weighing less than 10 kg and safety has not been established in sheep weighing less than 10 kg or under 2 weeks of age.

ZOLVIX is effective against strains of these parasites resistant to (pro)benzimidazoles, levamisole, morantel and macrocyclic lactones.

The main risk identified is the risk for dung fauna. This risk is apparent for dung droppings that are excreted during the first (approximately 3-4) days after treatment. After this period, the newly excreted dung droppings are considered safe for dung fauna. After a number of days, the ratio of safe and unsafe droppings will increase, hence the risk for the dung insect populations will decrease accordingly, allowing re-colonisation within a few days.

Nevertheless, although risks to dung insects were identified, in particular of dung excreted during the first 3 to 4 days after treatment, as the risk was present for a relatively short period and at a low level (dung insects are expected to be present in dung droppings of sheep previously at pasture which serve as a reservoir for insects to colonise droppings of treated animals within a few days) no risk management measures are considered necessary.

Monepantel possess a low toxicity without reproductive or teratogenic potential. It is not genotoxic. Sheep tolerance studies show that 10x maximum recommended dose of monepantel was well tolerated. There is no user risk when the product is used in line with recommendations in the product literature and it appears the environmental risk from the use of monepantel is limited to dung fauna. Risks to ground water, fresh water organisms or soil organisms have not been identified.

Care should be taken to avoid practices which could increase the risk of development of resistance and could ultimately result in ineffective therapy, for example too frequent and repeated use of anthelmintics from the same class, over an extended period of time or underdosage. In order to help delay the development of resistance, users are advised to check the success of the treatment (e.g. clinical appearance, faecal egg counts). Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Tests). Where the results of the tests strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.

With regard to residues it is agreed that the withdrawal period could be set at 7 days. ZOLVIX is not to be used in lactating animals producing milk for human consumption. Protective gloves should be

worn while handling the product and in case of accidental spillage onto skin or into eyes, wash immediately with water.

ZOLVIX has been shown to have a positive benefit risk balance overall and the benefits outweigh the risks. ZOLVIX has been shown to be efficacious for the indication as a broad spectrum anthelmintic for the treatment and control of gastro-intestinal nematode infections and associated diseases in sheep including lambs, hoggets, breeding rams and ewes.

The formulation and manufacture of ZOLVIX is well described and specifications set will ensure that product of consistent quality will be produced. It is well tolerated by the target animals and presents a low risk for users and the environment and where necessary appropriate warnings have been included in the SPC. A sufficient withdrawal period has been set.

The overall benefit risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature. Based on the original and complementary data presented, it is concluded that the quality, safety and efficacy of ZOLVIX were considered to be in accordance with the requirements of Council Directive 2001/82/EC, as amended.