SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Profender is a spot-on solution containing two active substances, emodepside and praziquantel, for topical use in cats. Profender was first authorised on 27 July 2005.

Emodepside is a member of a new class of cyclic depsipeptide compounds. It acts at the neuromuscular junction by stimulating presynaptic receptors belonging to the secretin receptor family, resulting in paralysis and death of the parasites.

Praziquantel, a pyrazino-isoquinoline derivative, is widely used in both human and veterinary medicines. It acts primarily by severely damaging the parasite integument resulting in contraction and paralysis, disruption of metabolism and finally death of the parasite.

Profender spot-on solution is presented in three different sizes of single-dose pipettes and also in a multi-dose bottle. The pipettes contain dose volumes of 0.35 ml, 0.70 ml and 1.12 ml for small, medium and large cats respectively. (Outer cartons of between 2 and 80 pipettes are available.) The multi-dose 14 ml glass bottle is supplied with a micro-spike adaptor which allows conventional small volume plastic syringes to be used for the withdrawal and accurate measurement of the required doses.

The approved indication is: "For cats suffering from, or at risk from, mixed parasitic infections caused by roundworms and tapeworms of the following species:

Roundworms (Nematodes):
Toxocara cati (mature adult, immature adult, L4 and L3)
Toxascaris leonina (mature adult, immature adult and L4)
Ancylostoma tubaeforme (mature adult, immature adult and L4)
Tapeworms (Cestodes):
Dipylidium caninum (adult)
Taenia taeniaeformis (adult)
Echinococcus multilocularis (adult)"

The benefits of Profender are its efficacy against adult tapeworms and various life stages of different roundworms. The most common side effects observed in the target species with the recommended dose were transient, and limited to salivation and vomiting. These signs are thought to occur as a result of the cat licking the application site immediately after treatment.

An extension application for a new target species (dogs), a new pharmaceutical form (modified-release tablets) and a new route of administration (oral use) for Profender was authorised in August 2008. Profender modified-release tablets for dogs contain emodepside and praziquantel and are available in three different strengths to cover a range of dog weights (small, medium or large dogs). The tablets have a break-line to facilitate breaking the tablet for accurate dosing. Profender tablets for dogs are supplied in laminated aluminium foil blister strips in an outer cardboard box. A variety of pack sizes are available for each tablet strength. The approved indication is "For dogs suffering from, or at risk from, mixed parasitic infections caused by roundworms and tapeworms of the following species:

Roundworms (Nematodes):
Toxocara canis (mature adult, immature adult, L4 and L3)
Toxascaris leonina (mature adult, immature adult and L4)
Ancylostoma caninum (mature adult and immature adult)
Uncinaria stenocephala (mature adult and immature adult)
Trichuris vulpis (mature adult, immature adult)
Tapeworms (Cestodes):
Dipylidium caninum
Taenia spp.
Echinococcus multilocularis (mature adult and immature)
Echinococcus granulosus (mature adult and immature)"

2. QUALITY ASSESSMENT

Composition

Profender spot-on solution contains 85.8 mg/ml praziquantel and 21.4 mg/ml emodepside dissolved in an organic solvent mixture, intended for topical administration by spot-on application to cats. All of the excipients have been employed previously in veterinary medicinal products. Butylhydroxyanisole is included as an antioxidant.

Profender modified-release tablets for dogs are light brown coloured, single scored, bone shaped tablets containing emodepside and praziquantel. The tablets are presented in three strengths; 3mg/15mg, 10mg/50mg and 30mg/150mg, each strength tablet has a score line to facilitate breaking the tablet for accurate dosing. All three tablet strengths are compressed from the same granulate to form tablets of different sizes; 3mg/15mg tablet (10 x 5 mm), 10mg/50mg (15 x 8 mm), 30mg/150mg (23 x 13 mm). The tablets include commonly used tablet excipients. These are all detailed in section 6.1 of the SPC.

Containers

Two different types of presentations of Profender spot-on solution are available:

1. Single dose white polypropylene plastic tubes with integrated seal membranes and polypropylene caps (which also acts as the opening device). The polypropylene is coloured white with titanium dioxide (E171) and the material of construction of the tube complies with the Ph. Eur. requirements for polyolefins (3.1.3). The accuracy and precision of pipette filling has been confirmed. Satisfactory specifications are provided.

   Secondary packaging comprises polyamide/aluminium/polyvinylchloride (OPA/AL/PVC) thermo-formed foil composite blisters (1 pipette per blister). Adequate specifications are provided.

   2, 4, 12, 20 or 40 pipettes in blisters are then packaged (with a package insert) into outer cardboard cartons. Additionally for the 0.70 ml pipettes there is an 80 pipette pack size.

2. Multidose 15 ml amber type II glass bottles sealed with a chlorobutyl rubber stopper and aluminium overseal. Each bottle is supplied with a micro-spike adaptor and package insert in an outer cardboard carton. The adaptor has a luer lock port and allows the appropriate dose to be withdrawn when used with a conventional small volume plastic syringe (not supplied). The adaptor remains attached to the bottle and is capped when not in use, thus the rubber bung is only pierced once. The suitability of the adaptor/syringe system has been demonstrated via accuracy and reproducibility data for withdrawal of representative volumes of product. The chlorobutyl rubber bung complies with the Ph. Eur. requirements for rubber closures for containers for aqueous preparations for parenteral use (3.2.9). Satisfactory specifications are provided for all primary packaging.

Profender modified-release tablets are supplied in polyamide/aluminium/polypropylene - aluminium foil blister strips placed in an outer cardboard box. A variety of pack sizes are available for each of the tablet strengths.

For both the spot-on solution and the tablets, compatibility of the primary packaging with the product has been demonstrated in the stability studies. Adequate specifications for all components are provided, as is batch data for a number of batches demonstrating compliance.

Development Pharmaceutics

Spot-on solution

Profender spot-on solution includes two active substances, emodepside and praziquantel, in a single endoparasiticide preparation. The aim of the pharmaceutical development was to produce a topical spot-on solution formulation because praziquantel is quite unpalatable and there are difficulties in masking its bitter taste. Spot-on formulations are now widely used for cats and have the advantage of ease of administration compared to oral tablets.

Both of the active substances have a low aqueous solubility, so an organic based formulation was necessary, the pH of which is controlled to optimise the product's stability. Butylhydroxyanisole (BHA, E320) is included in the formulation as an antioxidant as both actives are susceptible to oxidation. The chosen concentration was optimised during development studies. Selection of a suitable vehicle was based on the following: solubility and compatibility with the two active substances; toxicity and irritation; safety during manufacture; and release of the active substances into the skin and permeation through the stratum corneum (the rate limiting step in percutaneous absorption). Pharmaceutical development studies demonstrated that pH, water content and oxidation were critical factors influencing stability of the product. Packaging of the pipettes in individual blisters was shown to reduce permeability of the packaging and to prevent excessive increases in water content for the duration of the proposed shelf life.

The formulation is non-aqueous and the self preserving nature of the product has been demonstrated for both the pipettes and the multidose bottles. Preservative efficacy testing, in line with Ph. Eur. requirements for topical preparations, is presented and fully justifies the absence of an antimicrobial preservative.

The single dose pipettes have been widely used throughout the EU for the topical application of small volume veterinary medicinal products. Successful use over many years for other similar products confirms their suitability for purpose and as a consequence few development studies were performed. Product stability data confirms compatibility of the formulation and packaging materials. Furthermore, the primary packaging is confirmed as child-proof. Filling overages are defined for each pipette size in order to ensure that the stated dose can be expelled from each size of the pipettes.

The multidose bottles are intended for frequent users of the product such as in veterinary surgeries.

The formulation used in the pivotal clinical studies was identical to that proposed for marketing.

Modified-release tablets

In order to provide a broad spectrum activity against nematodes and cestodes in dogs, an oral solid dosage form was developed, as this is the simplest and most effective method for the treatment of parasites present in the GIT of dogs. The oral route of administration is also the preferred route for administering drugs to dogs.

Initial studies concentrated on the development of a standard immediate release tablet using conventional manufacturing techniques. Results of preliminary clinical trails determined that immediate release tablets were not suitable and so the focus moved to developing a controlled release tablet that would release 90% of the two active ingredients in 4-5 hours. Investigations using polymers that are erodible, and do not swell and stick together in an aqueous environment, proved successful and povidone was chosen as the retarding polymer for further investigations.

Povidone was the polymer found to achieve the desired release rate. Studies with early prototype formulations demonstrated that the residual moisture content of the granulate had a significant effect on compression force versus crushing strength and compression force versus disintegration time profiles. When three different tablet sizes were manufactured it was shown that the drug release rate became increasingly slower as tablet size increased however, these differences are acceptable from a clinical point of view.

The development of the dissolution method is described and fully justified. Dissolution limits at the initial timepoint are set to ensure that there are no excessively high plasma levels as they might lead to side effects. Limits at the final timepoint are set to ensure that there is complete release from the tablets. A tolerance limit is applied to the middle dissolution timepoint. The dissolution limits proposed are justified by data from several batches, including three batches which were used in the clinical studies.

One of the primary considerations in developing an oral dosage form was the masking of the bitter taste of praziquantel. For this reason, an irradiated artificial beef flavour was added to the formulation. Prototype formulations containing artificial beef flavour were subjected to palatability studies in order to optimise the concentration of flavour used.

The remainder of the excipients in Profender tablets are standard tablet excipients and were chosen to produce tablets of optimal hardness whilst facilitating the complete dissolution of the active substances. Physical characteristics and dissolution profiles (both actives) of the laboratory scale batches are also provided.

The formulation development rationale and data is accompanied by compatibility and stress test studies. No incompatibilities were found between the individual components of the formulation. Stress tests were performed on a pioneer formulation and the final formulation (flavour content was doubled in the final formulation with respect to the pioneer formulation). Results (hardness, assay, dissolution and disintegration) are provided from one batch of each formulation stored in several different stress storage conditions (e.g., 40ºC/75%RH and 60ºC/uncontrolled humidity) for differing time periods of up to a maximum of 10 months/45 weeks. These studies are early indicators of the reasonable stability of the product.

The effect of various manufacturing process parameters (residual moisture content present in the granules, quantity of water used for granulation, granulation time, dry mill sieve size, compression force, tablet size, etc) were also investigated and data provided. The reproducibility of the manufacturing process was also investigated.

Dissolution of both active substances becomes slower as tablet size increases. The size of the highest dose tablet was optimised using results from dissolution and friability studies. The primary rate determining step for dissolution of both active substances from the tablets was found to be disintegration of the tablet matrix.

As the tablets may be halved (to facilitate dosing), dose uniformity studies were performed on half tablets for all three strengths of the tablets. Half tablets complied with the requirements of the Ph. Eur. criteria in monographs 2.9.6.A, 2.9.5 and the harmonised monograph 2.9.40. The dissolution release profiles of half tablets were also investigated and shown to be only slightly different to whole tablets.

Method of manufacture

Spot-on solution

Manufacture of the bulk solution is a simple conventional operation and does not involve any non-standard processes. The active substances are dissolved in the solvents and antioxidant using mixing, then this solution is filtered and filled into bulk containers.

Within a period of 6 months after manufacture the primary packs (pipettes or glass bottles) are then filled from the bulk containers. The pipettes are sealed by heat or ultrasonics. After filling, the pipettes are packaged into blisters and sealed. Filling of the multi-dose bottles is a standard process.

The manufacturing formula for a typical batch size is presented. The in-process control tests ensure complete dissolution of the constituents and specify the controls applied during the filling process. These processes have been satisfactorily validated for the bulk solution and filling both container types.

Modified-release tablets

The bulk tablets are manufactured in the USA and then shipped to Germany for QC testing, assembly and batch release. Details of the packaging used for the bulk tablets is provided and justified.

The commercial batch size is stated. No overages are included in the formulation. The quantity of the active substances emodepside and praziquantel may be adjusted according to their purity with a corresponding adjustment in microcrystalline cellulose content.

Tablets are manufactured using a conventional wet granulation technique, followed by drying of the granules then addition of the post-granulation excipients and ultimately compression. A flow chart of the manufacturing process is provided along with a detailed description of the manufacturing process.

The in-process controls and frequency of testing are described and limits given (granulate: residual moisture) (tablets: thickness; single weights; hardness; friability; subdivision of tablets).

Although the product is a modified-release tablet, the manufacturing process is accepted as a standard one as no novel or complex manufacturing steps are involved. Formal process validation studies were not available on three full scale production batches at time of authorisation, but a commitment was provided which the CVMP considered (in conjunction with the data from production scale batches that had already been manufactured). The Committee concluded that satisfactory assurance with respect to the consistency of the manufacturing process had been provided and the commitment was acceptable.

CONTROL OF STARTING MATERIALS

Active substances

Emodepside:

Emodepside is not described in any pharmacopoeia. It is a semi-synthetic compound, the starting material for the chemical synthesis of which is produced by fermentation of the fungus *Mycelia sterilia.*

In the absence of a pharmacopoeial monograph emodepside is controlled by a comprehensive in-house specification. Methods are described and limits justified, where appropriate, for appearance, identity, purity, residual solvents (within VICH limits), water content, impurities (specified and unspecified, the limits for which are in line with VICH GL10), specific rotation, heavy metals and sulphated ash. Appropriate validation and batch data have been provided.

Nomenclature:

INN:	Emodepside
IUPAC Name:	Cyclo[D-2-hydroxypropanoyl-N-methyly-L-leucyl-3-[4-(4-morpholinyl)-phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)-phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl]
CAS number:	155030-63-0
Synonyms and abbreviations:	BAY 44-4400, PF1022-221, FR156742,
Molecular formula:	$C_{60}H_{90}N_6O_{14}$
Molecular weight:	1119.42

Description:

Appearance:	White to yellowish, odourless powder
Solubility in water:	pH 4 : 8.1 mg/l; pH 7 : 5.2 mg/l; pH 10 : 6.1 mg/l
Solubility in organic solvents (23°C):	Acetonitrile 48 %w/w; Ethanol 4%w/w; Methanol 1%w/w
Octanol:water partition coefficient:	log P_{ow} = 4.9 (pH 7)
Rotation:	-93° to -103°
Chirality:	8 chiral centres
Polymorphism:	Exhibits polymorphism

All steps of the manufacture of emodepside are well described. Starting materials are either fermentation derived (the main starting material) or purchased. The specifications and methods for the reagents, solvents and intermediates are appropriate and an adequate level of detail is provided. Synthesis comprises a four step process (full details of which are included in the dossier), followed by crystallisation and purification, prior to drying of the finished emodepside. Routine in-process controls are included at each stage of the process.

Adequate details of both process development and process validation have been provided.

Structural characterisation data (from elemental analysis, MS, ^{1}H NMR, ^{13}C NMR, IR, Raman, XRD and UV/Vis) is provided and the results and spectra are in agreement with the suggested structure. A detailed physicochemical characterisation is also included. Optical activity is present as emodepside contains 8 chiral centres (4 adjacent in alpha position to the carboxylic groups and 4 adjacent in the alpha position to the amide groups). The chiral properties of the molecule are introduced in the biosynthesis of the starting material, and remain fixed thereafter. Nucleophilic attack will result in ring opening by ester group cleavage, rather than by isomerisation because the basicity of the protons on these carbons is very low. As the active substance is fully dissolved in the final formulation, polymorphism is not relevant for this particular product.

In forced degradation studies, under a variety of stress conditions, solid emodepside was shown to exhibit moderate hygroscopicity. The stability of emodepside in solution under stress conditions resulted in dramatic degradation in basic conditions, while degradation under acidic and neutral conditions was less extensive. Solutions of emodepside are also susceptible to degradation following exposure to oxidative conditions and UV light, but remain relatively stable to thermal stresses.

Potential impurities arising from the route of synthesis/production/purification are discussed, identified, and levels obtained from 10 batches are detailed. With the exception of one isomer, all impurities are below the VICH qualification threshold of 0.5 %. The specified isomer is limited in the specification to 1.0 % and this has been justified.

Batch data from several pilot and full scale production batches of emodepside are provided and demonstrate compliance with the proposed specification.

Long term stability studies under VICH conditions have been performed on three batches of emodepside stored in metal drums with polyethylene liners. Test limits and stability indicating methods applied are the same as for release. Based on updated data provided for the modified-release tablets, a retest period of 36 months is considered justified.

Additional data on the emodepside reference standard materials were provided for the assessment of the modified-release tablets.

Praziquantel:

Praziquantel is purchased with an EDQM Certificate of Suitability (CEP). This includes the following additional tests, for which suitable methods have been provided:

Any other individual impurity (other than those specified in the monograph)	NMT 0.1 %
Chloride	NMT 0.02 %
Phosphate	NMT 0.05 %
Dichloromethane	NMT 600 ppm
Methanol	NMT 3000 ppm

The specification presented for praziquantel is designed to comply with Ph. Eur. requirements, as well as additional tests listed on the CEP, and is satisfactory to control the quality of this substance. Typical certificates of analysis for three batches are provided. All aspects of the certificates demonstrate compliance with the proposed specification.

An updated Ph. Eur. Certificate of Suitability for praziquantel was provided for the assessment of the modified-release tablets.

Stability data provided demonstrates praziquantel is a very stable active. Based on updated data provided for the modified-release tablets, a retest period of 48 months is considered justified.

Modified-release tablets

As both active substances are fully dissolved in the spot-on formulation their physical properties were not considered or included in the specifications. For the modified-release tablets however, the active substance specifications included limits for particle size and polymorphism which were justified by reference to development studies and clinical trials.

Excipients

Spot-on solution

Each of the components of the organic solvent mixture is tested in accordance with their respective pharmacopoeial monographs (either the Ph. Eur. or a pharmacopoeia of an EU Member State). Although not widely used in veterinary medicines, one of the solvents has been previously assessed by CVMP with respect to a maximum residue limit. It is therefore not considered to be novel, nevertheless, brief details of its manufacture have also been provided and are satisfactory.

Certificates of analysis for batches of each of the excipients demonstrate their compliance with their stated specifications.

Modified-release tablets

All the excipients, except the artificial beef flavour, comply with the relevant specification of the appropriate Ph. Eur. Monograph. Typical certificates of analysis are provided for each of the pharmacopoeial excipients demonstrating compliance with the relevant monograph.

The artificial beef flavour is not described in a pharmacopoeia but is widely used in other veterinary medicinal products authorised in Europe and is satisfactorily controlled by the proposed specification. It is composed of hydrolysed vegetable protein from soybeans, hydrogenated vegetable oil from soybeans and desiccated pork liver powder. The soybean derived components are sourced from non-GMO soybeans only. Full details of the sourcing of the pig livers and their subsequent processing were provided and considered satisfactory. The pig liver powder is sterilised by gamma-irradiation to eliminate the risk of transferring any viruses or microorganisms from pork liver to the target animal. Well defined, validated dose limits of 25-65kGy are used. The minimum dose limit of 25 kGy is in compliance with the EU guideline on the use of ionising radiation in the manufacture of medicinal products III/9109/90. All the necessary information on the gamma irradiation process is provided. A brief description of the manufacture of the artificial beef flavour is included. Routine tests and methods of manufacture have been described both for the artificial beef flavour and also for its components, and these were all acceptable. Certificates of analysis are also provided for two batches of the artificial flavour used in the clinical trial batches.

Immediate Packaging Material

Spot-on solution
See "Containers" above (page 2).

Modified-release tablets

Detailed specifications for both components of the primary packaging (white aluminium foil and PA/Al/PP laminate) have been provided and are acceptable. The specifications include appearance, identity, thickness and jointed sealing strength for the lidding foil and appearance, identity, and thickness of each layer for the base foil. Brief descriptions of the methods employed are included. The polypropylene used in the packaging material is shown to comply with the relevant monograph of the Ph. Eur. and with the EC Directive 2002/72 on plastic materials and articles intended to come into contact with foodstuffs. An IR spectrum of typical sample and reference standard are supplied. Certificates of analysis are provided for one batch of each component of the packaging.

Specific measures concerning the prevention of transmission of animal spongiform encephalopathies

Spot-on solution

Updated following a post-authorisation procedure (July 2007):
The product does not contain any substances of bovine, ovine or caprine origin. The active substance praziquantel is supported by a certificate of suitability issued in November 2002 and the Ph. Eur monograph relating to TSE will have been taken into account as part of this certification. The starting material for the synthesis of emodepside is the fermentation product PF 1022A which now is derived only from substances of non-animal origin.

Modified-release tablets

The product does not contain any substances of bovine, ovine or caprine origin. The active substance praziquantel is supported by a certificate of suitability issued in November 2002 and the Ph. Eur monograph relating to TSE will have been taken into account as part of this certification. The starting material for the synthesis of emodepside is the fermentation product PF 1022A which now is derived only from substances of non-animal origin. The artificial beef flavour is derived from human grade desiccated pork livers from documented and recorded sources and a comprehensive TSE risk assessment has been provided in relation to this material. Magnesium stearate is declared to be of non-bovine origin.

Control tests during production

Spot-on solution

The bulk solution is considered as an intermediate product and is stored in sealed stainless steel containers. A suitable specification is presented (with appropriately validated methods) and the proposed holding period of up to 6 months, before filling into the primary packaging, has been justified by stability data.

Modified-release tablets
Not applicable.

CONTROL TESTS ON THE FINISHED PRODUCT

Spot-on solution

Full details of the test methods in the release finished product specifications are presented in the dossier. The parameters included in the finished product specification are appropriate for a product of this type and include appearance, identity (each of the active substances and the antioxidant), assay, impurities, uniformity of mass, water content, microbiological quality and several appropriate physical parameters. All methods were suitably validated and the limits justified by reference to batch analyses data.

Modified-release tablets

Specifications (for both release and shelf-life purposes) and details of tests for the control of the finished product (including appearance; identity; water content; assay, expressed as mg per tablet; uniformity of dosage units; degradation products, specified, unspecified and total degradation products; dissolution rates of both the active substances; microbiological purity) were provided. The finished product specification is largely in line with the Ph. Eur. monograph for tablets.

Assay limits for both active substances are 95.0-105.0% of the nominal content. One degradation product of emodepside is identified on the finished product specification and limited to 1.0% w/w. Three known degradation products exist for praziquantel, however none of these are formed in significant amounts during stability testing and so are not specified on the finished product specification. Unspecified degradation products are also limited to 1.0% w/w and sum of all degradation products is limited to 4.5%. Degradation product limits at release are in line with VICH guidelines. Batch data from three clinical trial batches after 18 months storage at VICH conditions are provided in support of the proposed limits.

A single reversed phased gradient HPLC method has been developed for the identification and determination of emodepside and praziquantel and for the determination of the degradation products. The method has been validated in line with the relevant VICH guidelines.

The applicant has justified using the Ph. Eur. test for mass variation to demonstrate uniformity of dosage units in place of the content uniformity test as the RSD of the active substance in the final dosage units was shown to be not more than 2% based on data from the development and stability batches.

Dissolution limits are justified based on the functionality of the product and values obtained during stability studies for the three batches manufactured to the time of authorisation, but will be reviewed when more data becomes available and a follow up measure has been included to this effect.

Test methods are adequately described (mostly Ph. Eur. Methods) and representative chromatograms included where applicable. The validation data provided for each method are appropriate for the method and all acceptable. Details of the reference standards used in finished product testing are also provided and are satisfactory.

A declaration that the drug product has been assessed according to the VICH residual solvent guideline and found to be in compliance with the requirements is included in dossier.

Certificates of analysis are provided for the clinical trials batches (packed in both glass bottles and blister packs) in addition to the data provided for the stability batches packed in blister strips. All results comply with the specification. Degradant levels are consistent across all three tablet strengths.

Stability

Spot-on solution

The shelf life specifications differ slightly from those at time of release, as the lower shelf life limits for emodepside and praziquantel are widened slightly, as are the limits for both the impurity praziquantel B and an excipient stability-indicating impurity. These differences have all been justified by the stability data provided.

A primary stability study using VICH conditions has been undertaken, with samples of product packaged into each of the proposed presentations stored under long term and accelerated storage conditions.

Under real time and intermediate conditions both active substances and butylhydroxyanisole remain stable. Unspecified impurities (largest and total) remain at consistently low levels. Praziquantel impurity B levels remain below 0.2 % after 12 months at 30°C. Density, pH and water content are all consistent throughout the study. Colour of solution varies slightly in some batches.

Under accelerated conditions both active substances and butylhydroxyanisole remain very stable. Unspecified impurities (largest and total) remain at relatively low levels, albeit a little higher than under real time/intermediate conditions. Praziquantel impurity B levels are detected in the order of 0.3 – 0.45 % in all batches under accelerated conditions. Water content decreases in all presentations, by up to a quarter of initial values. Density and pH are consistent throughout the study. Colour of solution darkens slightly but remains within specification.

An in-use shelf life study was undertaken for the 14 ml multidose bottle. Five samples from two batches were broached and stored at ambient room temperature. Samples were broached weekly for 12 weeks and tested after 4, 8 and 12 weeks. The applicator supplied with the vial was used for the study and remained attached to the bottles for the duration of the study (as it would in practice). The study supports a 3 month in-use period and will be repeated with an aged sample at the end of the product shelf life. As the product has been demonstrated to be self-preserving and there is no deterioration of the product following broaching, the lack of preservative efficacy data as part of the study was justified.

Modified-release tablets

The finished product shelf-life specification has a number of changes with respect to the release specification. The limits for water content, one specified degradation product and total degradation products are increased and justified (and for the degradation product qualified by toxicity studies). Assay limits for emodepside have been widened, which is justified as a slight decrease in active substance content is seen on storage in parallel with an increase in degradation products. No limits are included in the specification for praziquantel degradation products, however, these are covered by the “any unspecified degradation product” (max. 1.0) and “total degradation products” (max. 5 %).

36 months real time stability data on a number of batches, stored at a variety of conditions in accordance with current VICH guidance, along with 6 months accelerated data and the stability profile is presented. All results for the batches packed in blister packs remain with the proposed specifications and demonstrate good stability of the product. Supporting stability data from tablets stored in glass bottles also demonstrate reasonable stability of the product. Assay values show some degree of variability with a trend of decrease for both active substances after storage at 30ºC/70%RH and 40ºC/75%RH. No significant change is observed after 6 month storage at the accelerated storage condition of 40ºC/75%RH, and as such no storage precaution in relation to temperature is required. Slight increases in unspecified degradation products are seen in parallel with the decreases in active substance content although all remain within their specified limits. The reduction in the lower assay limit on the shelf-life specification is therefore considered justified.

The dissolution rates for emodepside and praziquantel become moderately faster with increasing storage time and temperature, particularly for the smaller tablets, but all results remain well within the specification.

The light sensitivity of these modified-release tablets was also investigated. The tablets were exposed to irradiation in the primary packaging material and in the primary packaging material tightly packed in aluminium foil (in accordance with the VICH Guideline on Stability testing: Photostability testing of new veterinary drug substances and medicinal products). No significant decrease in active substance content or increase in degradation products was observed and it is concluded that the product is not photolabile.

A shelf-life of 36 months, with no storage temperature restrictions, is justified and accepted.

Although an in-use stability study was performed, the CVMP considered the dosage regimen specified in the SPC (i.e. single treatment) and decided it was not appropriate to assign an in-use shelf-life to these tablets after opening the immediate packaging as for both safety and quality reasons unused half tablets should not be stored for future use. The Committee agreed a statement to this effect to be included in the SPC, labelling and package leaflet accordingly.

OVERALL CONCLUSION ON PART 2

Spot-on solution

The manufacture of the dosage form is adequately described and controlled, in accordance with current guidance. The data provided demonstrate that product of the desired quality is consistently produced. The product does not contain any substances of bovine, ovine or caprine origin. The quality data provided are satisfactory and adhere to current guidelines.

There is no need to protect either the single dose or the multidose product from light when in their marketing packs. The proposed shelf life for the finished product (3 years, with no storage restrictions) is supported by the stability data presented, as is the 3 month in-use shelf life for the multi-dose bottle.

Modified-release tablets

The quality of the modified-release tablets is adequately established and there are no major deviations from current EU and VICH requirements. The excipients are all commonly used in veterinary tablet formulations and all comply with current Ph. Eur. requirements except the artificial beef flavouring, for which a satisfactory in-house specification was provided, along with full details of its manufacture and control. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described.

The control tests on the finished product specification cover the relevant quality criteria and are adequate to confirm adequate and consistent product quality. Dissolution limits are justified.

Stability tests under VICH guidelines conditions indicate that the product is chemically stable for the proposed shelf-life (36 months, with no storage temperature restrictions).

3. SAFETY ASSESSMENT

The safety profile of the active substance praziquantel was previously assessed by CVMP at the time of the initial MRL assessment for this compound. Thus, where appropriate, the MRL Summary Reports for praziquantel (published on http://www.emea.europa.eu/htms/vet/mrls/a.htm) have been referred to; only new studies are described below.

The data below were mainly provided for the original marketing authorisation application (for Profender spot-on for cats) and then cross-referred to in the application for the modified-release tablets for dogs. However, where some additional data were provided in the latter application that were not part of the original application, this has been indicated.

PHARMACODYNAMICS AND PHARMACOKINETICS

See section 4 of this EPAR.

TOXICOLOGICAL STUDIES

Single dose toxicity

The Applicant has submitted the results of a number of studies for emodepside in rats and mice; for praziquantel in mice, rats, rabbits and dogs; and for the combination in rats.

Both emodepside and praziquantel appear to be of low acute toxicity in a variety of laboratory animal species, and by a variety of routes. Although overt signs of toxicity include depressed neurological and respiratory function, they only occur at dose rates far in excess of the recommended therapeutic dose (RTD) in the cat.

Repeated dose toxicity

Emodepside

All studies were GLP-compliant and well conducted. The adverse effects of treatment on clinical signs, body weight gain, haematology/biochemistry and necropsy observations were remarkably consistent from study to study. The studies presented have accurately and consistently identified the repeat-dose toxicity profile of this compound.

Four repeated dose toxicity studies after oral administration of emodepside were conducted in rats and mice for up to 17 weeks. The effects shown in these studies include reduction in weight gain; effects on neurological function, behaviour and respiration; reduction in the absolute weight of the testes; increase in the relative weight of the brain in male rats; ataxia; increased motility; piloerection; increase in glucagon-secreting cells with a trend towards significant hyperglycaemia; polydipsia and polyphagia. The liver (increased enzyme activity and reduced protein synthesis), adrenal glands, pancreas and reproductive system were the principal target organs for toxicity.

Studies in cats, dogs, mice and rabbits, however, showed no significant or consistent hyperglycaemia nor altered metabolism of fat and proteins or increase in food consumption. It is noteworthy that many histopathological changes did not reverse during the 4-week recovery period. From these studies in rats, the NOEL was 0.73-1.11 (subchronic) and 4.4-4.6 (subacute) mg/kg bw. In mice, the NOEL was 10.5-16.8 mg/kg bw.

A repeated dose toxicity study of emodepside after dermal application was performed in rats, with an observation period of 4 weeks. There was no significant increase in erythema or in skin fold thickness. However, histopathology revealed mild acanthosis and inflammatory cell infiltration. Systemically, there were discoloured faeces and increased production of both urine and faeces at the highest dose level. A NOEL of 100 mg/kg bw can be retained for the study.

Modified-release tablets for dogs:

One new study for emodepside was submitted in this application, a GLP compliant subacute oral toxicity study in dogs which were given emodepside doses of 0, 5, 10, 20 mg/kg bw daily orally by gavage daily for 4 weeks, with 4 week recovery period.

The main findings noted were a decrease in food intake during week 4 in two females at 20 mg/kg bw. No such effects were observed in males. Body weight gains were slightly reduced in males at 20 mg/kg bw and in females at ≥ 10 mg/kg bw. However, body weight gain of high-dose animals (males and females) was comparable to that of the controls during the 4 week recovery period. Increased ESR, leucocyte and neutrophil counts were observed in one high-dose female at week 4. There were no significant differences in most clinical chemistries investigated. Some liver enzyme values were mildly decreased in treated males and females; however, the changes recorded were deemed slight, highly variable and frequently without dose-dependency.

There were no mortalities throughout study. With regards to clinical observations, there were no significant effects on reflexes, body temperature, blood pressure, heart rate and ECG findings. However, increased episodes of vomiting and tremor/ataxia were noted in males at dose rates ≥ 10 mg/kg bw. Females exhibited tremor/ataxia at ≥ 10 mg/kg bw, with staggering, incoordination and reduced overall health status at 20 mg/kg bw. The NOAEL for this study was 5 mg/kg bw.

Although this material is considered of secondary importance compared to the target animal tolerance data (in part 4), the CVMP noted that there was a low incidence of tremor/ataxia in low-dose males (5 mg/kg bw). Although the low incidence of this had been highlighted, the Committee believes this finding to be the beginning of the trend noted at higher dose rates and it was proposed not to retain a NOEL from this study.

Praziquantel

Some studies were already considered by the CVMP at the time of the initial MRL application for this active substance. For further details, please refer to MRL Summary Reports for praziquantel. All studies were non GLP-compliant, although study design was reasonable in each case for the time in which they were conducted. Only one new study is presented here.

Repeated dose toxicity of praziquantel after dermal application was investigated in rabbits with an observation period of 3 weeks. Despite the presence of proteinuria and parasitic infections in the liver, no adverse effects of treatment were observed. The dose tested (500 mg/animal) was identified as a NOEL in this study.

Reproductive toxicity

Emodepside

No two-generation study was presented investigating the reproductive toxicity of emodepside in rodents or rabbits. However a GLP-compliant one-generation pilot study, investigating reproductive performance in rats, was available to the Committee. Even in light of the adverse effects on reproductive and endocrine tissues that were observed in the repeat-dose toxicity studies conducted in rodents, the omission of such studies was considered justified based on the results of the tolerance study performed in pregnant cats (see section 4 of this EPAR).

Praziquantel

A series of three studies were presented, each of which had been considered previously by the CVMP when the MRLs were set for praziquantel. For further details, please refer to MRL Summary Reports for praziquantel.

Despite the limitations in relation to the perinatal and postnatal toxicity studies, the use of praziquantel in breeding cats is unlikely to impair fertility, particularly in light of the fact that all dose rates were well in excess of the RTD in the cat. Previous experience of this molecule in a number of species has not highlighted any specific concerns in this regard.

Modified-release tablets for dogs:

No new data was presented. There is no information available on the effects of emodepside in breeding dogs but as clear information is included in the SPC and product information that the safety of the product has not been investigated in pregnant and lactating dogs, and that the use of the products in these dogs is therefore not recommended, the Committee considered this approach justified.

Embryotoxicity/foetotoxicity, including teratogenicity

Emodepside

In rats, both the ovarian weight and the gestation rate were unaffected by treatment. Clinical signs of systemic maternal toxicity were evident at dose rates ≥ 6 mg/kg bw. Overall, severe maternal toxicity at 18 mg/kg bw resulted in adverse effects on foetal development. The NOEL for maternal toxicity was 2 mg/kg bw and the NOEL for developmental toxicity was 0.5 mg/kg bw.

In rabbits, the effects were similar to the rat studies. The NOEL for developmental toxicity in the rabbit was 5 mg/kg bw.

In addition to the rodent study specified above, the safety of emodepside during pregnancy was also investigated at excess dose levels in the target species (cat). On the basis of these two studies and the user safety risk assessment, the CVMP was satisfied that a single time point administration of the test product during pregnancy is likely to be well tolerated in the target species, and that the risk of reproductive toxicity to end users is low. Nevertheless, there are no data on the effects of treatment on general reproductive performance in breeding cats. A battery of well-conducted, GLP-compliant teratogenicity studies revealed a fairly consistent pattern of maternal toxicity, foetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. Taking the sum of all studies, the NOEL for developmental toxicity could be set at 0.5 mg/kg bw for the rat and 5 mg/kg bw in the rabbit. Although these studies involved repeated administration, it should be noted that the dose level in the rat was well below the RTD in the cat. The CVMP concluded that the issue was best addressed in the SPC (section 5.12) where the following statement has been included: “Although the product was well tolerated by pregnant cats, studies performed in rats and rabbits suggest that emodepside may interfere with embryo-foetal development. Therefore, women of child-bearing potential should avoid contact with, or wear disposable gloves when administering the product”.

Praziquantel

In addition to one published report (Ni *et al.*, Mutagenic and Teratogenic Effects of Anti-schistosomal Praziquantel, Chinese Medical J. 95: 494-498, 1982), the studies presented under this heading have previously been assessed by the CVMP. For further details, please refer to the MRL Summary Reports for praziquantel.

A further review article by Olds (Administration of praziquantel to pregnant and lactating women, Acta Tropica, 86: 185-195, 2003) was submitted. This review article looked at the available data relating to the use of praziquantel in pregnant women, lactating women and adolescent females. The author argued strongly that the data available from the widespread use of this compound in humans in schistosomiasis eradication campaigns supports the use of praziquantel in pregnant and lactating women, irrespective of the absence of specific safety studies. The author states that available pharmacovigilance data suggest that the potential for adverse effects on either the mother or the unborn foetus is very low.

Praziquantel appears to exert no significant effects on fertility indices at dose rates well in excess of the RTD. The available evidence also suggests that praziquantel is not teratogenic.

Modified-release tablets for dogs:

No new data was presented. There is no information available on the effects of emodepside in pregnant dogs but as clear information is included in the SPC and product information that the safety of the product has not been investigated in pregnant and lactating dogs, and that the use of the products in these dogs is therefore not recommended, the Committee considered this approach justified.

Mutagenicity

Emodepside

A battery of appropriate *in vitro* and *in vivo* tests indicates that emodepside is a non-mutagenic substance.

In a micronucleus test on the male mouse, observations of animals treated twice at 100 mg/kg bw or more included: apathy; running round in circles; roughened fur; loss of weight; staggering gait; sternal recumbency; spasm; twitching; shivering; difficulty in breathing; and partially closed eyes.

Praziquantel

The mutagenic potential of praziquantel was assessed previously by the CVMP. For further details, please refer to the MRL Summary Reports for this substance.

Whilst there are various reports suggesting a co-mutagenic or co-carcinogenic role for praziquantel, as concluded by CVMP previously, the available data would suggest that praziquantel itself has a low primary mutagenic potential. The positive findings for sister chromatic exchange (SCE) in certain *in vitro* studies were not reflected in the corresponding *in vivo* chromosomal aberration assays.

Carcinogenicity

Emodepside is a semi-synthetic compound belonging to a new class of molecule (depsipeptides). The CVMP is unaware of the existence/non-existence of any data relating to structural alerts for this family of compounds. In view of the fact that both emodepside and praziquantel are considered to have low direct mutagenic potential, and in the absence of any reported concerns following more than two decades of use of praziquantel in various species (including man), full-term carcinogenicity studies for the combination were not considered necessary.

Skin and eye irritation

Emodepside

In rabbits, emodepside was found to be non-irritating (patch test) to the skin and not to be acutely irritating (instillation into conjunctival sac) to the eye.

In guinea pigs, emodepside was found to have no skin sensitisation potential.

Praziquantel

An investigation in the rabbit indicated that praziquantel was minimally irritating to skin, but mildly irritating to the eye in terms of corneal opacity.

Praziquantel was not allergenic following repeated application to human volunteers (topically) and guinea pigs (intradermally).

Combination studies

A patch test in the rabbit demonstrated that the combination of emodepside and praziquantel was non-irritating to skin. A study in guinea pigs showed that the combination was non-sensitizing to skin (topical and intradermal).

An acute eye irritation study by instillation into the conjunctival sac of the rabbit showed that the combination was mildly irritating to the eye and conjunctivae; however, all lesions had regressed by 96 hours post-instillation.

Immunotoxicity

No data were presented under this heading. Reference was made to the lack of effects on lymphoreticular tissues in the repeat dose studies.

Endocrinology

A study for subchronic oral toxicity of emodepside in rats (hormone determination in female rats, feeding study for 28 weeks and 14 weeks recovery) was carried out. Many of the toxicological findings were similar to previous studies. It was noteworthy that the reduced body weight gains did not correct during the recovery period. The potent effects of emodepside on endocrine function were observed during treatment, although hormone concentrations returned to normal during the recovery period. The influence of treatment on ovarian function included increased numbers of corpora lutea and persistent oestrus, although the high dose rate is well above the RTD for the cat. Oestradiol levels were reduced (if in persistent oestrus) and progesterone levels were not increased (if high numbers of corpora lutea). From the data on thyroid hormones, the administration of emodepside in rats at the highest dose is noted to suppress the total T3 level, in both a time- and dose-dependent manner, with a tendency towards increased T4 and TSH hormone levels.

The above study also included a review of the results of three additional in vitro studies investigating the effects of emodepside on sex steroid receptors, which indicated that emodepside had no effects or affinity for the receptors concerned.

Phototoxicity

An article by Shao et al. (1986) reported that slight phototoxic reactions (erythema and swelling) were seen in mice exposed to UV radiation 24 hours after gavage of > 2180 mg praziquantel/kg bw. However, a similar effect was not observed at a dose rate of 1600 mg/kg bw. Phototoxic reactions subsided markedly within 72 hours.

Combination toxicity

In general, the clinical signs observed in an acute toxicity study in rats after oral administration of emodepside and praziquantel were more severe and lasted longer than those caused by the administration of each individual active. Thus, toxicity was defined as being super-additive. Although the effects of the combination were more than simply cumulative, the doses employed were huge in comparison to the RTD in the target species.

Microbiological studies (studies on human gut flora and organisms used in food processing)

There are no antimicrobial properties known for either active ingredient.

Studies on metabolites, impurities, other substances and formulation

A comprehensive set of data were presented to address these issues. The most relevant information were as follows:

- Butylated hydroxyanisole (BHA) – acute toxicity was very low, except when administered by the intraperitoneal route. This compound is mildly irritating to skin and eye but only at high concentrations. The target organs for BHA toxicity are the liver, kidney and GI tract (rodents). BHA is not teratogenic. BHA was associated with tumour formation in the forestomach of rats and Syrian Hamsters. Studies in dogs, pigs and monkeys did not indicate a carcinogenic potential. It should be noted that the doses concerned were well in excess of those present in the formulation for Profender.
- Solvent in the formulation – effects were noted on CNS function and blood pressure (hypotension) but only at high concentrations. LD_{50} values were very high (variety of routes). Mutagenicity and teratogenicity studies were negative.
- Lactic acid – this is a normal intermediate metabolite in the body and exhibits low acute and chronic toxicity potential by the oral route. At concentrations present in pharmaceutical/cosmetic formulations, lactic acid was non-irritating or mildly irritating to the eye. There was no evidence of any teratogenic, mutagenic or skin-sensitizing effects.

Modified-release tablets for dogs:

In addition to cross-reference to the previous data, a non-GLP-compliant Salmonella Ames test screening study was presented to demonstrate the safety of emodepside degradation product A (hydroxyethylemodepsid). The results showed that doses of hydroxyethylemodepsid up to and including 3,200 µg per plate did not cause any bacteriotoxic effects. This result was confirmed with a full and GLP-compliant Salmonella microsome test. The compound was also tested in a chromosome aberration test, showing it is not clastogenic *in vitro*. The Committee agreed with the conclusion that hydroxyethylemodepsid was neither mutagenic nor clastogenic under the conditions of these assays.
A repeated-dose study in rats showed no impact of the degradation product on the toxicity of emodepside.

User safety

Spot-on solution:

Worst-case assumptions based on oral or dermal contact have been calculated. The calculations were based on the results of the acute and repeat dose toxicity studies presented above, and two additional studies outlined below:

- A specific study investigating the ability of children to open the proprietary tubes with twist-caps was conducted according to national requirements in existence in Germany. The results met the required criteria.

- A study to investigate the possible amounts of both active ingredients that could be removed from treated cats using standardised stroking techniques was also performed. The highest amounts of emodepside and praziquantel removed occurred at the 30-minute post application stroking period, with mean values of 0.5 mg and 1.45 mg, respectively.

The calculations established that the theoretical safety margin in each scenario was well in excess of 100-fold. The SPC advice included under section 5.12 contains pertinent information to try and minimise dermal or oral exposure.

There is currently no information in relation to emodepside in man. However, the high LD_{50} values, and the absence of any irritation/skin sensitisation potential for emodepside in the animal safety studies provide a significant margin of comfort in this regard.

Many of the published reports dealt with the use of praziquantel in man to control schistosomiasis in endemic areas. In general, the risk-benefit ratio of praziquantel has long been considered favourable, and the molecule is still extensively used on a worldwide basis. The tolerance data in healthy volunteers demonstrated that a dose rate of 75 mg/kg bw per os produced a transient disturbance in general well-being that was not evident at 50 mg/kg bw. The available genotoxicity data presented under this heading were limited, but suggested that praziquantel did not significantly contribute towards any mutagenic findings in patients with spontaneously occurring parasitic diseases. In general, despite various reports of drug interactions and potential co-mutagenic properties, the risk-benefit ratio of praziquantel has long been considered favourable, and the molecule is still extensively used on a worldwide basis.

Modified-release tablets for dogs:

A comprehensive user safety assessment (in compliance with the relevant guideline) was provided as part of the application for the modified-release tablets for dogs. For most exposure scenarios, it is not expected that the product will pose a risk to users. However, the Committee acknowledged that there is a potential risk to young children should they ingest unused/part-used tablets, particularly if a small child were to ingest a tablet for large dogs. For both safety and quality reasons therefore the CVMP agreed that advice should be included in the SPC and product information that any unused half tablets should not be stored for future use.

Environmental safety

Spot-on solution:

An Environmental Risk Assessment (Phase I) was performed and the following scenarios considered:

- Washing cat after treatment - This is considered a very unlikely event. Additionally the wording in the SPC section 5.10 clearly discourages washing or shampooing the cat after treatment. In any case washing water would run into municipal disposal systems and be heavily diluted to extremely low concentrations. Exposure of the environment via this route is therefore regarded as not relevant.

- Contamination of watercourses/ponds - When cats stray outside they usually avoid water and try not to get wet. Therefore exposure by this route is also considered not relevant.

- Disposal of unused product - This is a relevant scenario for environmental contamination due to the toxicity of emodepside to water fleas. Disposal of the unused product should therefore avoid contamination of watercourses, as this may be a risk for aquatic arthropods. A suitable warning is therefore included in section 6.5 of the SPC so that the product should not be allowed to enter watercourses and any unused product or waste materials should be disposed of in accordance with local requirements.

In conclusion, the CVMP were satisfied that the environmental risk assessment for this product stops at Phase I of the Decision Tree, as the product is clearly intended for individual animal treatment involving a companion animal species.

Modified-release tablets for dogs:

A Phase I assessment was provided for the application for the modified-release tablets for dogs. This examined the physical/chemical structure of the product and the indications for use in line with the SPC. In addition, use of the Phase I decision tree of the relevant guideline was employed. This approach resulted in the assessment stopping at Step 3 of the phase I decision tree. The Committee accepted that the use of the product in accordance with the label recommendations would not pose a risk to the environment.

OVERALL CONCLUSIONS ON SAFETY

Emodepside is a new active substance and has a low acute toxicity by a variety of routes. Repeat dose studies indicate abnormal clinical signs (neurological, demeanour, piloerection etc.) and adverse effects on water/feed consumption, liver enzymes, glucose levels, etc. The liver, adrenal glands, pancreas and reproductive system were the principal target organs for toxicity. Not all changes in blood values or organ weights/morphology were reversible in the studies conducted. Although potent effects on various endocrinological end-points were identified, emodepside does not appear to interact directly with androgenic or oestrogenic receptors. However, tolerance studies (see section 4 of this EPAR) indicate that the problems identified above were largely absent at the level of the target species. The effects of emodepside on general reproductive performance in breeding animals are unknown. Whilst a battery of developmental toxicity studies identified adverse effects in rats and rabbits, use of the molecule in pregnant cats (see section 4 of this EPAR) has not been associated with any teratogenic findings. Emodepside appears to have a very low mutagenic potential. Although no carcinogenicity data were provided, the negative results in the mutagenicity studies indicate that such studies are not be required. Emodepside is non-irritating to the eyes and skin, and does not appear to be a skin sensitising agent.

Praziquantel is a well-established active and its safety profile has not altered appreciably from the initial CVMP assessment conducted at the time of the MRL application. The molecule has a low acute and repeat-dose toxicity profile by both the oral and dermal routes. Target organs for toxicity include the liver, kidney and thyroid gland. Praziquantel does not appear to adversely affect reproductive performance, and is not teratogenic. The long-term use of praziquantel in several species (including man) has not highlighted any carcinogenicity concerns. Although this compound may cause mild irritation to the eyes, it does not appear to be a skin sensitising agent. The only significant concerns raised in man relate to the potential co-mutagenic effects of praziquantel, although some studies demonstrated a protective effect against mutagenicity/carcinogenicity in various helminth diseases of man. Although praziquantel is relatively more toxic when combined with emodepside, the doses required for adverse clinical signs are well in excess of the RTD in the cat.

The user safety of the combination product has been adequately addressed.

A satisfactory Phase I environmental impact assessment was performed.

Limited new data submitted were provided in the application for the modified-release tablets for dogs. This consisted of a new repeat dose safety study in the dog, tolerance studies in the target species (see part 4) and a Salmonella Ames study was presented for the safety of emodepside degradation product A (hydroxyethylemodepsid).

The only area of concern from the new data relates to the low incidence of tremors/ataxia in the low-dose group in the repeat dose safety study in beagles. However, from the point of view of target animal safety, more emphasis should be put on the studies submitted in Part 4. Safety in breeding and pregnant animals was not assessed, so the SPC and product information contains advice against use in pregnant and lactating dogs.

An environmental risk assessment was performed, and no risks to the environment following use of the product are anticipated.

A user safety assessment was performed and the final product information reflected the results of this.

4. EFFICACY ASSESSMENT

Pharmacodynamics

Emodepside

Emodepside is a semi-synthetic compound belonging to the new chemical group of depsipeptides and has been shown to exert high efficacy against a wide variety of adult nematodes in animal species including mice, rats, poultry, dog, cat, cattle, sheep and the horse. Action against larval stages of nematodes is reported to vary according to the species.

It acts at the neuromuscular junction by stimulating the presynaptic Latrophilin receptors belonging to the secretin receptor family which results in paralysis and death of the parasites.

It is noted that emodepside may have an effect on vasodilation in dogs when administered by the intraduodenal route at a dose of 1.5 mg/kg bw. Effects on glucose metabolism were seen in rats after oral administration of 3 mg/kg bw. In addition, it is noted that emodepside administered orally at high doses elicited abnormal behaviour in rats (characterised by decreased locomotor activity as well as posture and gait abnormalities): these effects were seen at doses of 30 and 100 mg/kg, with a NOEL of 10 mg/kg.

A further study was conducted on the interaction of emodepside with the multi-drug resistant protein (MDR). Compared to ivermectin, emodepside is more effectively effluxed in MDR-1 cells and this active transport is not saturable in the concentration range tested. These data suggest that emodepside will not be able to cross membranes such as the blood brain barrier. However, given that there is the potential for interaction with other P-glycoprotein dependent substrates, an appropriate warning statement has been included in Section 5.7 of the SPC.

Praziquantel

Praziquantel is an acylated pyrazino-isoquinoline derivative. Praziquantel is active against cestodes and trematodes. It acts primarily by severely damaging the parasite integument resulting in contraction and paralysis, disruption of metabolism and finally death of the parasite.

In a number of studies, praziquantel administered in various formulations and at a variety of dose rates (e.g. intramuscularly at 5 mg/kg; topically as a spot-on at 8 mg/kg), has been shown to be an effective treatment for the major cestode species, including *Echinococcus spp.*, in cats and dogs.

The mode of action of praziquantel is well documented and has been satisfactorily described.

Pharmacokinetics

Emodepside

Pharmacokinetics was studied following I.V. administration in the rat. In summary:

- approximately half the administered dose was excreted in the first 24 hours, with the remainder being excreted slowly, with up to 8 % still being detected at 168 hours,
- faecal excretion predominated with only 2-3 % of the dose being found in urine,
- the elimination half life was calculated to be 39-51 hours,
- the bioavailability was 53-57 % at both dose levels,
- the highest levels of radioactivity were found in the fat, at all dose levels and time points, which was probably acting as a depot for the absorbed radioactivity,
- unchanged emodepside was the major excretion product, accounting for 45-56 % of the dose. There are numerous small metabolites with only 4 groups accounting for >5 % of the dose.

In addition to the pivotal ADME study in the rat, reports of other studies were provided. The principle observations were:

- In two subacute toxicity studies in rats, emodepside was administered in the food. Blood concentrations were comparable on days 9 and 28 suggesting that steady state had been reached by day 9. While there appeared to be dose proportionality between the low and medium dose group, there appeared to be some degree of saturation between the middle and high dose groups.
- When a formulation of the active substance in ethanol was applied enterally to dogs, the highest mean plasma concentrations were found in the 5 and 15 mg/kg group 1 hour after application, whereas T max was reached after 0.5 hours for the 45 mg/kg group. It is noted that Cmax increased proportionally up to 15 mg/kg. Thereafter, a saturation of absorption became apparent.

Praziquantel

The data provided support the pharmacokinetic profile as represented in the CVMP MRL Summary Reports for praziquantel. For further details, please refer to these.

Combination products

Spot-on solution for cats:

A pharmacokinetic study in cats was conducted in Europe with the formulation intended for marketing. Two applications were administered topically at the base of the skull at monthly intervals.

A high inter-individual variability of the pharmacokinetic variables was observed. After topical application of the test product to cats at the minimum therapeutic dose of 0.14 ml/kg bw, mean serum concentrations (Cmax) of approximately 32.5 µg emodepside/L and 59 µg praziquantel/L were observed. Maximum concentrations were reached at about 2 to 3 days after application for emodepside and at <12 h for praziquantel. Both active substances are then slowly eliminated from the serum with a half-life of about 9 days (emodepside) and about 4-5 days (praziquantel).

The profile of the mean serum concentration for emodepside indicated two peaks following each treatment. It is therefore likely that emodepside was partially distributed from the central compartment into another compartment (probably fat) and from there slowly redistributed to the systemic circulation.

The data indicate that minimal accumulation of emodepside may occur in association with monthly administration of the product. However, it is not proposed that the product be administered at this frequency.

A local application site (involving also the skin of the ventral chest) adverse reaction was detected in one cat. However, in that case, no skin lesions were seen for the first four days after treatment, but emerged subsequently on day 5 and were also seen beyond the application site. Therefore, it is not clear that the reaction was treatment related. A slight whitish deposit was seen in some cats at the application site 2-14 days after the treatment. Otherwise, the treatments were well tolerated.

Modified-release tablets for dogs:

The pharmacokinetic profile of emodepside and praziquantel when administered in combination orally to dogs was characterized as part of a GLP target animal safety study. For both substances, the concentration-time profile of the mean serum concentrations indicated rapid absorption following oral administration. After reaching a peak, concentrations of both substances declined with a half-life of 1.4 to 2.5 hours. A high inter-individual variability of the pharmacokinetic variables was observed. It is noted that concentrations of both substances achieved in plasma were dose proportional. It is evident that accumulation of emodepside does not appear to occur in association with repeated treatment every two weeks.

In a non-GLP study conducted to investigate the influence of food on pharmacokinetics of emodepside and praziquantel following oral administration, it was demonstrated that maximal emodepside concentration was nearly twice as high when dogs were fed compared to when not fed. Similarly, AUC_{0-12} was markedly higher in the fed state compared to the unfed state. Effects of feeding on emodepside Cmax and AUC_{0-12} were statistically significant. For praziquantel, maximal serum concentrations were lower in unfed dogs compared to fed dogs. However, timing of feeding in relation to treatment did not have a marked impact on praziquantel AUC_{0-12} values. The effect of feeding on praziquantel Cmax was statistically significant. From the target animal safety studies (product administered at multiples of the recommended treatment dose), it appears that the severity of adverse effects (tremor, ataxia) is greater when dogs are fed compared to when not fed. Based on the findings of the present study, the observation in the target animal safety (TAS) study would appear to be linked to the higher serum concentrations of emodepside achieved when dogs are fed at the time of treatment. The SPC therefore includes the following recommendation “Administer only to fasted dogs. For example overnight fasting is recommended if the dog is to be treated in the morning. Food may be given 4 hours or more after treatment.”

Impact of resistance development to efficacy

The two active ingredients are not related structurally to one another, and the spectrum of activity and mode of action of each is discrete, so it is unlikely that the presence or development of resistance to one active would impact on the usefulness of the other.

This is the first time that emodepside has been used as an anthelmintic and it comes from a new class of anthelmintics that has not been used before. The field study in cats represented the first time that non-laboratory helminths had been exposed to this class of anthelmintics. Thus it is extremely unlikely that resistance exists: it has certainly not been reported, and would not be anticipated in the near future.

Praziquantel has been widely used as a cestocide for over a decade, and the data presented indicate that resistance is not a concern at the present time.

However, as with all anthelmintics there is the potential for resistance to develop to one or both actives in the future, so appropriate use and monitoring of apparent treatment failures will help to ensure that resistance does not develop quickly and is recognised when it does occur.

Notwithstanding the lack to information to indicate resistance to either of the actives the following standard warning statement is included in the SPCs (section 4.4) and product literature for both the spot-on for cats and tablets for dogs: "Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class."

Target animal safety

Spot-on solution for cats:

A series of studies were performed to investigate the tolerance of cats to the application of the test product (final formulation).

In a study using the test product topically in young cats, the adverse effects related to the product administered in overdose included salivation, emesis and tremors. These were few relative to the total number of treatments and were both mild and transient. Although the dermal treatment site was difficult to reach for the animals, oral ingestion of the test product could not always be prevented, in particular when large (overdose) volumes were applied. It is suggested that these signs were a result of post treatment oral exposure. Consequently, it can be accepted that the product was well tolerated when administered repeatedly at two-week intervals for 6 occasions at doses up to 5 times the recommended treatment volume. Plasma glucose concentrations in test animals were evaluated as part of this study, and no treatment related effect on this parameter was observed in any of the treatment groups. No application site reactions were noted. These data suggest that any tendency for emodepside accumulation is not likely to give rise to safety concerns.

In another study using the test product topically in young cats, the product was generally well tolerated when administered by the recommended route at 10 times the recommended dose volume. Mild salivation was transiently present in a number of cats. It is probable that the cats licked the application site and salivation was induced following contact of the oral mucosa with the topical solution. In addition, muscle tremor (sign of possible mild neurotoxicity) followed by depression was noted in one cat in the 10x dose group. These signs were observed approximately 24 hours post treatment, but had resolved within a further 24 hours. The report states that this animal had been observed grooming and that it is probable that an amount of test product was ingested. No application site reactions were noted.

A safety study investigated the recommended dose of the product given orally to cats. It is accepted that oral exposure to this amount of the product is an extremely unlikely event in the field. While adverse effects were observed in all animals that were administered the product, these effects (salivation and vomiting) were transient. These signs are natural defence mechanisms that are activated upon exposure to an oral irritant and, as such, are expected clinical signs resulting from oral ingestion of a topical solution containing organic solvents.

Repeated dermal treatment with up to 3 times the recommended dose, during pregnancy and lactation, was tolerated by queens without effects on general conditions or changes in laboratory parameters, on reproductive parameters, on kitten viability or on kitten rearing, and without indication of a foetotoxic or teratogenic potential. Adverse effects on reproductive function of the dams and/or kitten health are therefore not to be expected when the product is administered at the recommended treatment dose.

A study using the product with selamectin or moxidectin showed that the product was well tolerated and that the concomitant administration of either selamectin or moxidectin/imidacloprid did not appear to impact negatively its safety profile.

Based on these data, the CVMP accepts that the product is safe for administration to cats at the recommended treatment dose. Appropriate warning statements have been included in Section 5.4 of the SPC.

Modified-release tablets for dogs:

A comprehensive range of GLP-compliant studies were performed to investigate systemic tolerance of the target species, dogs, to the administration of the test product. All studies were conducted using the final formulation.

The predominant adverse effects observed that were considered treatment related were neurological, in particular muscle tremor. The frequency and severity of muscle tremor tended to increase with increasing dose and was accompanied by in-coordination and behavioural changes in some dogs. Typically, such effects were transient, resolving without treatment within 8 hours. Section 4.10 of the SPC includes information on the clinical signs that may be observed when the product is administered in overdose.

In the pivotal target animal safety study (test product administered to unfed pups), it is noted that tremor (classed as 'slight') was a common occurrence following the first administration of the test product. This is considered to be linked to the age (9-11 weeks at the time of first administration) and size of pups. For later treatments in the pivotal study and in other studies conducted, slight tremor was recorded infrequently in pups receiving the recommended treatment dose (RTD) and when it occurred was classed as slight, such that it was not possible to clearly establish whether this finding was caused by treatment. Based on the information presented, the CVMP accepts that the product is well tolerated when administered at the recommended treatment dose to fasted pups of 12 weeks and older. Consequently the SPC includes a contraindication for use in pups less than 12 weeks old or weighing less than 1 kg (section 4.3).

Based on the information provided, it is clear that the incidence and intensity of adverse effects is greater when the product is administered as an overdose (3X or 5X the RTD) to fed pups or in conjunction with feeding, compared to when the product is administered to fasted pups. This effect appears to be related to the pharmacokinetic profile of emodepside in fed dogs: maximal emodepside concentration was nearly twice as high when dogs were fed compared to when not fed. Similarly, the AUC was markedly higher in the fed state compared to the unfed state. Effects of feeding on emodepside Cmax and AUC were both statistically significant. Given that adverse effects were detected in fed pups at 3X the RTD, it is not possible to conclude on a margin of safety for the product when administered to fed pups. The SPC includes both advice and a warning (see sections 4.5 and 4.9) that the product should be administered only to fasted dogs and that food should only be given 4 hours or more after treatment. The Committee accepts that this recommendation is appropriate. It also noted that no treatment related adverse effects were recorded in the field study, in which the timing of product administration in relation to feeding was not regulated.

Vomiting (small amounts) was recorded for a number of dogs in two studies where dogs were fed directly after treatment with 3X or 5X the RTD, such that a treatment related effect for vomiting in fed dogs also cannot be ruled out. Section 4.10 of the SPC includes appropriate advice to this effect accordingly.

The CVMP considered that the safety of the product when administered at the recommended treatment dose is supported by the results of the clinical efficacy studies. In the field study conducted to investigate safety and efficacy of the final formulation (see part 4), 239 client owned dogs (variety of breeds, ages, gender) were treated with the combination product according to the proposed dosing regimen. Dog owners fed the dogs in accordance with normal habits (that is, timing of treatment in relation to feeding was not regulated). No adverse effects attributable to treatment were observed in that study. Similarly, in the numerous other clinical studies conducted to investigate efficacy of the test product, the product was well tolerated. While it is acknowledged that these studies will have used the minimum recommended treatment dose, it is reassuring to note that no effects that could be attributed to treatment were observed. In the clinical efficacy studies, occasional gastrointestinal signs (in particular, loose faeces/diarrhoea) were recorded. Typically, these effects were noted in both control (placebo) and test product treated groups and in many cases were noted pre- and post treatment.

It is suggested that the changes in faecal consistency in some dogs may be the result of the parasitic infection. In addition, it is suggested that, in dogs that are administered the test product, dying worms after treatment may release toxins that affect gastrointestinal function, thereby resulting in gastrointestinal signs. It is noted that the gastrointestinal effects observed in this series of studies are transient and are of limited clinical significance. Whatever the cause of the altered faecal consistency in these studies (product administered at the minimum RTD), the Committee accepted that the effect is not treatment related at the dose of product administered.

Based on the available data, the Committee accepted that the product is safe for administration to dogs at the recommended treatment dose. The principle adverse effects when the product is administered in overdose are neurological signs (muscle tremor, in-coordination, behavioural change) and these effects are transient, resolving without treatment within 8 hours. Clear advice is included in section 4.10 of the SPC that feeding can increase the incidence and intensity of overdose symptoms, and that occasionally vomiting may occur.

A specific study investigated the safety of emodepside/praziquantel tablets in Collie dogs that were homozygous for the *mdr1* mutation (which is responsible for avermectin sensitivity). Based on the findings of this study, the test product was well tolerated when administered at a dose of 1.6 mg emodepside and 8 mg praziquantel per kg. However, it is noted that the safety margin in *mdr 1* mutant (-/-) Collie dogs appears to be lower compared to dogs that do not have the mutation (that is, mild transient tremor and/or ataxia were occasionally observed at 2 x RTD). Therefore section 4.10 (overdose) of the SPC includes advice about the lower safety margin in this group of Collies.

Safety has not been investigated in pregnant or lactating bitches, therefore use in this category of dog is not recommended and the SPC and product literature includes clear advice to this effect.

In the field studies concomitant treatment included mainly vaccines and antibiotics. No tolerance studies were performed in severely debilitated dogs or in dogs with seriously compromised kidney or liver function. Therefore the CVMP concluded that the following standard warning statement should be included in section 4.5 of the SPC (Special precautions for use; Special precautions for use in animals) “No studies have been performed with severely debilitated dogs or individuals with seriously compromised kidney or liver function. Therefore, the veterinary medicinal product should only be used in such according to a benefit/risk assessment by the responsible veterinarian.”

Dose determination studies

Spot-on solution for cats:

In all the studies the test product was administered topically at the back of the neck. The pivotal dose determination studies were conducted using *Toxocara cati* and *Dipylidium caninum*. The Applicant suggested that the use of these parasites in the pivotal studies was justified on the basis that they are dose-limiting species.

A study on the efficacy of emodepside against artificial infection with *Ancylostoma sp.* in cats in South Africa concluded that emodepside was effective against *Ancylostoma braziliense* at doses of 2 and 4 mg/kg. No adverse reactions related to the application of the test products were observed during the study.

The efficacy of emodepside at various doses against natural infection with *Ancylostoma spp*. and *Toxocara spp*. in cats in Australia was conducted with a GCP-compliant study. The results demonstrated that 2 mg emodepside/kg was highly effective against naturally acquired infections of *Ancylostoma spp.* and/or *Toxocara spp*. No adverse events attributable to treatment were observed.

The evaluation of the efficacy of three dosages of emodepside (administered in combination with praziquantel) against artificial *Toxocara cati* infection in cats in South Africa was conducted with a GCP-compliant study. All test doses confirmed emodepside was highly effective against artificial *Toxocara cati* infection. *Dipylidium caninum* was detected in one cat in the low dose treatment group (1.5 mg/kg emodepside, 6 mg/kg praziquantel). Some slight local application site reactions were observed (barely perceptible erythema with greater numbers in the highest dose group and slight desquamation in one animal). No other treatment related effects were observed.

The evaluation of the efficacy of different dose levels of a combination of emodepside and praziquantel against mature *Toxocara cati* in cats was carried out with the final formulation in USA with a GCP-compliant pivotal study (controlled test). The doses of emodepside ranged from 1.5 to 6 mg/kg and of praziquantel from 6 to 24 mg/kg. All test doses were highly effective (100%) against mature and immature adult *Toxocara cati* infection. The test product was well tolerated and no systemic or local application site reactions were observed.

In a South African study for dose determination against *Dipylidium caninum* in cats, a dose of 12 mg praziquantel/kg was found to be 100 % effective. However, this dose was ineffective against *Joyeuxiella spp.* No treatment related adverse effects were observed.

In a second South African GCP-compliant study for the dose determination against *Dipylidium caninum* in cats, the treatment with praziquantel at doses of 10 and 12 mg/kg was 100 % effective against infection. No treatment related adverse effects were observed.

A pivotal GCP-compliant controlled study for the dose determination of praziquantel against *Dipylidium caninum* was conducted in South Africa. The dose range for emodepside was 1.5 to 6 mg/kg and for praziquantel was 6 to 24 mg/kg. Efficacy of treatment with praziquantel administered at doses of 6 mg/kg was 94.83%, of 12 mg/kg was 90.04% and of 24 mg/kg was 100%. No adverse events attributable to treatment were observed.

A study to investigate the efficacy of emodepside and praziquantel against immature and mature *Echinococcus multilocularis* in cats was conducted in Australia. The test formulation at 8 mg praziquantel/kg was highly effective for the removal of both immature and mature (prepatent) *Echinococcus multilocularis* from cats. No adverse events attributable to treatment were observed. Two cats were observed scratching at the application site for a short period (minutes) after treatment.

An evaluation of the efficacy of different dose levels of a combination of emodepside and praziquantel against natural *Dipylidium caninum* infection in cats was carried out. This was a GCP study conducted with the final formulation in South Africa. In this study, *Taenia* scolices were not found in cats treated with praziquantel at 12 mg/kg or over. Some cats in the groups treated with the product were co-infested with Toxocara cati or Ancylostoma spp. and no worms were found in any of these cats. It is accepted that treatment with a combination of 3 mg or more of emodepside and 12 mg or more of praziquantel per kg bodyweight was 100 % effective against Dipylidium caninum in this study. The test product was well tolerated and no systemic or local reactions were observed.

Based on the dose determination studies, 12 mg praziquantel/kg was shown to be effective against *Dipylidium caninum* and 3 mg emodepside/kg was shown to be an effective dose for *Ancylostoma* and *Toxocara*.

Dose confirmation – *Toxocara cati*

A total of 4 GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against *Toxocara cati*. Two studies investigated efficacy against adult *Toxocara cati*, whereas the other two studies investigated efficacy against L4 and immature stages. In all studies, the adequacy of infection for concluding on the efficacy of the product was considered satisfactory. It is noted that three of the four studies investigated efficacy against artificial infections: two of those were conducted in the EU (Germany) using a German strain of *Toxocara cati*.

The final formulation was found to be 100 % effective against adult *Toxocara cati* in the cat. In addition, it can be accepted that the product is 100 % effective against L4 and immature adults. However, the original data submitted in support of the claim for efficacy against L3 larval stages were not considered sufficient. In response to a request from the CVMP, the Applicant provided an additional study as supportive data. Test animals were artificially infected with *Toxocara spp.* eggs on day 0 and treated with the test product on day 7. Treatment at day 7 was aimed at migrating larvae, which may be either L3 or L4. At the end of the study, no worms were found in the test product group whereas a mean (geometric) of 33.8 worms was detected in the control group. Based on the findings of both studies, the claim for efficacy against *Toxocara cati* L3 can be accepted.

One of these studies investigated the potential for interference between active substances in the formulation. The results indicate that praziquantel does not appear to interfere with the anthelmintic activity of emodepside against *Toxocara cati*. Similarly, given that there was no statistically significant difference in worm burdens of the placebo group compared to the group that received praziquantel only, it was concluded that praziquantel does not have an anthelmintic effect against *Toxocara cati.*

Generally, the test product was well tolerated. In one study, one placebo treated cat exhibited salivation and tongue ulceration which began 8 hours after treatment. It is unclear as to whether this was a reaction to oral contact with the placebo.

Dose confirmation – *Toxascaris leonina*

A total of 4 GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against *Toxascaris leonina*. Two studies investigated efficacy against mature adult stages, whereas the other two studies investigated efficacy against L4 and immature stages. It is noted that all four studies investigated efficacy against artificial infections and all were conducted in the USA.

A feature of these studies was the difficulty in establishing adequate levels of infection: this was a particular problem in the studies designed to evaluate efficacy against L4 and immature adult stages. Notwithstanding the difficulties in establishing adequate infections, it can be accepted that, when taken as a whole, the data are sufficient to support the claim for efficacy against L4, immature adult and mature adult stages of *Toxascaris leonina*. Although none of the studies described above investigated efficacy versus European isolates, further justification for the claim against *Toxascaris leonina* was provided. The technical difficulties in establishing adequate infection with European isolates was highlighted. In view of the difficulties encountered, and given the fact that the efficacy of the product against US isolates has been proven in a number of studies, the claim for activity against *Toxascaris leonina* is considered justified.

It is noted that in all studies conducted, the test product appears to have been well tolerated.

Dose confirmation – *Ancylostoma tubaeforme*

A total of 5 GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against *Ancylostoma tubaeforme*. Three studies investigated efficacy against adult stages, whereas the other two studies investigated efficacy against L4 and immature stages. In all studies, the adequacy of infection for concluding on the efficacy of the product was considered satisfactory.

None of these studies investigated efficacy versus European isolates, as three of the five studies were conducted outside the EU and the other two studies, although conducted in the EU, used *Ancylostoma tubaeforme* isolates that were sourced outside the EU. However, efficacy was demonstrated against isolates from three different continents (Australia, Africa and America). Given the disparate origins of those isolates it would not be expected that significantly different results would be obtained by using European isolates.

Furthermore, in the field study, all cats with confirmed *Ancylostoma* infections were treated with the test product and 100% efficacy was achieved. Although these numbers are insufficient for statistical analyses, it is considered that the findings in the field study serve as adequate confirmation of the results obtained in the dose determination/confirmation studies.

The final formulation was found to be highly effective and it is considered that the data are sufficient to support the claim for efficacy against L4, immature adult and mature adult stages of *Ancylostoma tubaeforme*.

No systemic or local adverse effects relating to treatment were observed. No abnormalities were observed at the application site.

Dose confirmation – *Dipylidium caninum*

A GCP study showed that praziquantel at the recommended dose is effective against natural *Dipylidium caninum* infection in the cat. Emodepside does not appear to have an anthelmintic effect against *Dipylidium caninum* and does not interfere with the anthelmintic activity of praziquantel. No adverse events attributable to treatment were observed. This study, together with the pivotal dose determination study, is considered sufficient to support the claim for efficacy against adult stages of *Dipylidium caninum*. While both of these studies were conducted outside of Europe, it is accepted that praziquantel has been used in Europe as an effective treatment for cestode infections in companion animals for many years; therefore, it is expected that European isolates of *Dipylidium caninum* will continue to be susceptible to praziquantel.

Dose confirmation – *Taenia taeniaeformis*

Three GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against *Taenia taeniaeformis* when administered at the minimum recommended treatment dose. These studies investigated efficacy in cats naturally infected with the parasite. All three studies were conducted outside the EU.

These results of these studies are considered sufficient to support the claim for efficacy against adult stages of *Taenia taeniaeformis*. While these studies were conducted outside of Europe, it is accepted that praziquantel has been used in Europe as an effective treatment for cestode infections in companion animals for many years; therefore, it is expected that European isolates of *Taenia taeniaeformis* will continue to be susceptible to praziquantel.

Dose confirmation – *Echinococcus multilocularis*

Three GCP studies were conducted to investigate the efficacy of the final formulation against *Echinococcus multilocularis* in the cat. In addition, a fourth study using an exploratory formulation was performed. Based on these data, a claim for efficacy against mature stages can be justified given that:

- In two GCP studies the product was shown to be 100 % effective against mature (21-day-old) stages when the product was administered at the minimum recommended therapeutic dose. In both of these studies, the *Echinococcus multilocularis* isolates originated from Germany.
- In a preliminary study, an exploratory formulation was shown to be 100 % effective at a dose rate of 8 mg praziquantel per kg.
- In the third GCP study, efficacy against mature stages was only 98.5%. In this study, the *Echinococcus multilocularis* isolate originated from the USA. It is not clear why the test product did not achieve 100 % efficacy in this study. However, when all the available data are taken together, it is considered that efficacy “approaching 100 %” has been achieved.

Modified-release tablets for dogs:

A series of published documents relating to the epidemiology and prevalence of endoparasites found in dogs in Europe was provided in support of the justification for the combination. In reviewing this information, the CVMP noted that:

- Precise information relating to the prevalence of dog helminth infections is difficult to obtain.
- Typically, this information relates to specific countries or regions within a country, such that individual reports cannot be considered representative of the whole of Europe.
- Some of the surveys are dated and may not reflect the current situation.
- Information relating to prevalence is generally based on faecal examination, which is not very reliable for the determination of cestode infestations.

Justification for the formulation:

- In addition to their potential to cause illness in the dog, a number of dog helminths are important zoonotic pathogens and as such are a potential hazard to public health.
- The test product has a broad spectrum of activity, with claimed efficacy against the common nematodes and cestodes of the dog. Based on pivotal study data (non-interference studies) presented with the application, it has been confirmed that emodepside is solely responsible for effect against nematodes and praziquantel is solely responsible for effect against cestodes. In addition, it has been shown that neither product interferes with the activity of the other.
- Emodepside has not been used previously for the treatment of helminth infections in the dog and has a novel mode of action. Its introduction broadens the spectrum of anthelmintics available for dog, therefore decreasing reliance on anthelmintics currently in use.
- The tolerance to the constituent active substances, when administered in combination, has been investigated extensively in the target species.

It was noted that, in the field study submitted with the application, 3.2 % of dogs with a confirmed gastrointestinal helminth infection had a mixed nematode/cestode infection. Notwithstanding the relatively rare occurrence of mixed infections (at least based on those data), the Committee accepted that broad-spectrum anthelmintic products are useful and consequently was satisfied with the justification provided. Indeed, it was noted that there are many combination products authorised nationally in all Member States on the basis that they provide a broad spectrum of activity and that the tolerance to the constituent active substances, when administered in combination, has been investigated. Furthermore, the combination emodepside/praziquantel is already authorised as a topical formulation for use in the cat.

The principle efficacy criterion in the majority of the clinical studies was based on a comparison of the numbers of the target parasite recovered at necropsy from treatment groups compared to the control groups. For all the studies, the adequacy of infection was evaluated in line with the recommendations of the relevant VICH guideline. Typically, for individual parasite stages the number of dogs in the control group (placebo) with an adequate infection ($\geq$ 5 worms) was required to be at least 6 dogs.

Based on data form the literature and their experience working with tapeworms, the Applicant suggests that *Echinococcus* and *D. caninum* require similar doses of praziquantel that are higher than the dose required for *Taenia* spp. It is suggested that *Taenia hydatigena* can be considered as a dose limiting *Taenia* species. Based on the data presented, it has been shown that praziquantel is effective against natural *D. caninum* infection when administered at doses of 2.5 mg and 5 mg/kg bodyweight. Despite confirmation of efficacy against *D. caninum* at a dose of 2.5 mg/kg, the standard oral dose of 5 mg praziquantel/kg bodyweight was retained as the minimum recommended treatment dose. The CVMP acknowledged that 5 mg/kg can be accepted as the standard oral dose for praziquantel.

A series of pilot studies using development formulae were conducted to identify an effective dose of emodepside in the dog. The target species investigated were *Uncinaria stenocephala*, *Ancylostoma caninum* and *Trichuris vulpis*. In this series of studies, emodepside, when administered at a dose of 0.5 mg/kg had acceptable efficacy against *U. stenocephala* and *A. caninum*. However, this dose was only 73.7% effective against *T. vulpis*. Based on these data, 1.0 mg emodepside was chosen as the minimum effective dose for further studies and *T. vulpis* was considered a dose limiting species. Efficacy against *T. vulpis* at a dose of 1 mg emodepside/kg was demonstrated in a further pilot study.

In a pivotal GCP study, efficacy against mature and immature adult *T. vulpis* was investigated at 0.5X, 1X and 2X the RTD: Emodepside was 99.6% and 100% effective against immature adult and adult *T. vulpis* respectively at a dose of 0.5 mg/kg (that is, half the recommended treatment dose). While 0.5 mg emodepside/kg was shown to be effective in the pivotal study, the Committee could accept the decision of the Applicant to choose 1.0 mg emodepside as the minimum effective dose based on the findings of earlier studies.

Dose confirmation – Nematodes

A series of GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against nematodes when administered at the minimum recommended treatment dose. In accordance with the relevant VICH guideline, to be granted a claim, the following pivotal data should be provided:

- Two dose confirmation studies, with a minimum of 6 adequately infected non-medicated, control animals,
- Differences in parasite counts between treated and non-medicated, control groups should be statistically significant and
- Effectiveness, based on geometric means, should be 90% or higher.

The criteria detailed above have been satisfied for the following nematode species (stages):
- *Toxocara canis* (mature adult, immature adult, L4 and L3)
- *Toxascaris leonina* (mature adult, immature adult and L4)
- *Ancylostoma caninum* (adult and immature adult)
- *Uncinaria stenocephala* (adult and immature adult)
- *Trichuris vulpis* (adult and immature adult).

The CVMP accepted that efficacy of emodepside, when administered orally at a dose of 1 mg/kg, against those stages has been confirmed.

In addition to the data submitted with the application, and in response to the list of questions, the Applicant conducted three further dose confirmation studies in support of the efficacy of the product against larval stages of *T. canis* and *T. leonina.* For *T. canis,* >90% efficacy against L3/L4 was demonstrated in two of three studies and for *T. leonina* >90% efficacy against L4 was demonstrated in two of three studies. Pooling of data from the three *T. canis* L3/L4 efficacy studies resulted in an overall efficacy of 93.3%. Similarly, pooling of data from the three *T. leonina* L4 efficacy studies resulted in an overall efficacy of 95.9%. Based on the totality of data presented by the Applicant, the CVMP accepted that satisfactory efficacy has been demonstrated against immature stages of *T. canis* (including L3/L4) and *T. leonina* (including L4).

One of the dose confirmation studies investigated the potential for interference between active substances in the formulation. The results indicate that praziquantel does not appear to interfere with the anthelmintic activity of emodepside against *T. vulpis*, *U. stenocephala* or *A. caninum* in the dog. Similarly, given that there was no statistically significant difference in worm burdens of the placebo group compared to the group that received praziquantel only, it was concluded that praziquantel does not have an anthelmintic effect against *T. vulpis*, *U. stenocephala* or *A. caninum*.

It is noted that in all studies conducted, the test product appears to have been well tolerated.

Dose confirmation – Cestodes

One GCP-compliant dose confirmation study was conducted to confirm efficacy of the final formulation against each of the claimed target cestodes when the test product is administered at the minimum recommended treatment dose (1 mg emodepside and 5 mg praziquantel/kg). The studies were conducted in accordance with current guidelines and praziquantel at a dose of 5 mg/kg administered orally was confirmed to be effective against *Dipylidium caninum*, *Taenia spp.* (*T. hydatigena*), *Echinococcus multilocularis* and *E. granulosus*. In the studies conducted, the test product was 100% effective against:
- *Dipylidium caninum*,
- *Taenia* spp. (*T. hydatigena*),
- *Echinococcus multilocularis* (mature adult and immature)
- *E. granulosus* (mature adult and immature)

While single studies only were conducted to investigate the efficacy against the claimed cestode species, it is noted that praziquantel has been used in Europe as an effective treatment for cestode infections in companion animals for many years and that the standard oral dose for the dog is 5 mg praziquantel/kg bodyweight. In addition, based on the finding of the *D. caninum* study, it has been demonstrated that emodepside does not appear to have an anthelmintic effect against *D. caninum*. Similarly, emodepside does not interfere with the anthelmintic activity of praziquantel against *D. caninum*.

The data presented in relation to the claimed cestode species is accepted as adequate.

CLINICAL STUDIES

Spot-on solution for cats:

In a GCP-compliant multi-centre field study conducted in the European Union, the safety and efficacy of the test product was evaluated in cats naturally infected with intestinal nematodes (Ascarididae and Ancylostomatidae) and/or cestodes (Taeniidae and Dipyliidae). The control product contained selamectin. Of the cats enrolled in the study, only 4.79 % harboured a mixed nematode/cestode infection. However, adequate data were available to conclude that the test product was safe and efficacious (>90 %) in the treatment of nematode (especially *Toxocara cati*) and cestode (especially *Dipylidium caninum* and *Taeniidae spp.*) infestations in naturally infested cats. There is also evidence of efficacy against *Toxascaris leonina* and *Ancylostomatidae*. The test product was as efficacious against nematode infection as the control product. It was shown that the product is well tolerated under field conditions of use.

Modified-release tablets for dogs:

One large GCP field trial was provided to evaluate the efficacy and safety of Emodepside plus Praziquantel in dogs naturally infected with intestinal nematodes (*Ascarididae, Ancylostomatidae, Strongyloididae, Trichuridae*) and/or cestodes (*Dilepididae, Taeniidae* and *Diphyllobothriidae*) and to assess the prevalence of mixed infestations of intestinal nematodes and cestodes in dogs in a clinical field trial. The multi-centre, controlled, randomised and blinded field trial was carried out in four EU counties and involved 33 veterinary practices. Test animals were 354 client owned dogs (various breeds); 170 female, 184 male; 5 weeks to 19 years; 2.0-75.5 kg in weight. Profender modified-release tablets were given orally at a minimum dose of 1 mg emodepside and 5 mg praziquantel per kg bodyweight. The reference product was oral tablets of milbemycin oxime and praziquantel, at a minimum dose of 0.5 mg milbemycin oxime and 5 mg praziquantel per kg bodyweight.

Dogs (with diagnosed intestinal nematode and/or cestode infestations) were randomly allocated to one of two treatment groups and administered either the test product or the reference product (two dogs received the test product for every one that received the reference product). The products were administered orally once on Day 0. There were no special requirements/restrictions relating to feeding. The post treatment observation period for a single study animal was 7 to 13 days.

Faecal samples were collected once between day –7 and day 0, then a second and a third faecal samples were collected between days 7 and 13. All faecal samples were examined for eggs of intestinal nematodes and/or cestodes and for the presence of cestode proglottids. Clinical observations were made once before treatment observation on Day 0 and again once at the end of the study period (between days 7 and 13 post treatment). Adverse events during the study period were either observed by the investigator or reported by the owner. The primary efficacy criterion in the evaluation of efficacy for nematodes was the reduction in faecal egg count from pre-treatment to Day 7-13 post-treatment. If one or both of the post treatment faecal egg counts were above zero, the higher value was used for calculation of efficacy. The primary efficacy criterion in the evaluation of efficacy for cestodes was the reduction in faecal egg count from pre-treatment to Day 7-13 post-treatment and the presence or absence of proglottids post treatment. If one or both of the post treatment faecal egg counts were above zero, the higher value was used for calculation of efficacy. The efficacy of the test product was assessed for non-inferiority by comparing post baseline faecal egg counts of nematode and cestode infection and the presence or absence of proglottids (for cestodes infection only) to the control group.

A total of 2237 animals were screened of which 354 animals confirmed positive for nematode and/or cestode infection were enrolled into the study and were treated with either the test product (n=239) or the reference product (n=115). This population was used as the 'intent-to-treat' population and was used for the assessment of safety. The two treatment groups were comparable.

After treatment administration on Day 0, the examining veterinarian evaluated the acceptance of the dog to the tablet administration procedure. The percentage of the 'intent-to-treat' population showing good acceptance to treatment was 79.5% for the test product and 63.5% for the reference product.

No treatment-related local or systemic adverse effects were observed following administration of either the test or the control product.

The 'Per-protocol' population was made up of 288 animals that fulfilled the protocol requirements and had not been subject to any deviation that affected the validity of the data. Of this population 192 were administered the test product, with 96 receiving the reference product. This population was used for evaluation of efficacy.

Of the 288 dogs in the per-protocol population, only 11 (3.8 %) harboured a mixed nematode/cestode infection.

Nematodes

For dogs treated with the test product, the reduction in faecal nematode egg counts was 99.9% (95% confidence interval: 99.8-100.0%). This is compared to a reduction of 99.6% (95% confidence interval: 99.3-99.8%) for dogs treated with the control product. The non-inferiority of the test product to the control product was confirmed.

Efficacy against nematodes (all species)

	Emod/praziquantel (n=163)		Milbemycin/praziquantel (n=84)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	473.5	-	416.2	-
Post-treatment	0.5	99.9%	1.62	99.6%

Efficacy against nematodes (*Trichuris vulpis*)

	Emod/praziquantel (n=89)		Milbemycin/praziquantel (n=51)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	462.4	-	386.2	-
Post-treatment	0.5	99.9%	1.6	99.6%

Efficacy against nematodes (*T. canis*)

	Emod/praziquantel (n=37)		Milbemycin/praziquantel (n=17)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	241.7	-	218.1	-
Post-treatment	0.2	99.9%	0.4	99.8%

Efficacy against nematodes (*Uncinaria Stenocephala*)

	Emod/praziquantel (n=57)		Milbemycin/praziquantel (n=34)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	307.3	-	362.5	-
Post-treatment	0.0	100%	1.6	99.6%

Efficacy against nematodes (*Ancylostoma caninum*)

	Emod/praziquantel (n=29)		Milbemycin/praziquantel (n=10)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	369.9	-	476.8	-
Post-treatment	0.2	100%	2.7	99.4%

Cestodes

The reduction in cestode faecal egg counts was 100% in both treatment groups. Again, non-inferiority was confirmed.

Efficacy against cestodes (faecal egg count reduction)

	Emod/praziquantel (n=15)		Milbemycin/praziquantel (n=5)	
	Geometric mean	% Efficacy	Geometric mean	% Efficacy
Pre-treatment	702.7	-	487.4	-
Post-treatment	0.0	100%	0.0	100%

Efficacy against cestodes (presence of proglottids)

	Emod/praziquantel (n=32)		Milbemycin/praziquantel (n=11)	
	No. of animals	%	No. of animals	%
Pre-treatment	32	100	11	100
Post-treatment	0	0	0	0

Based on the results of this study, the Committee concluded that the test product is highly effective against patent nematode (*Toxocara canis, Trichuris vulpis, Ancylostoma caninum* and *Uncinaria stenocephala*) and cestode infections in the dog. It is noted that there is also evidence of efficacy against other nematode species, however, subpopulation analysis could not be performed due to low numbers of animals infected with these species. It was accepted that the test product was as effective as (non-inferior to) the control product, milbemycin oxime with praziquantel, against nematode and cestode infections in the naturally infected dog.

The Committee also agreed that the product is well tolerated under field conditions of use. In this study, 239 client owned dogs (variety of breeds, ages, gender) were treated with the combination product according to the proposed dosing regimen. Dog owners fed the dogs in accordance with normal habits (that is, timing of treatment in relation to feeding was not regulated). No adverse effects attributable to treatment were observed.

Concomitant treatments (within four days either side of treatment) were administered to 57 dogs in the clinical efficacy studies. No evidence of intolerance was detected. However, the numbers of dogs exposed to individual treatments were small. Therefore it is not possible to conclude definitively on compatibility with other veterinary medicinal products based on these limited data.

Data relating to a number of animals were not used for the evaluation of efficacy because of deviations to the protocol. The reasons for the removal of these data have been reviewed and are considered justified.

A supportive two phase cross-over blinded palatability study (from South Africa) presented an evaluation of the palatability of six tablet formulations containing emodepside/praziquantel or febantel/pyrantel/praziquantel and a commercial dog biscuit treat. All dogs were more than 6 months old and were predominantly cross-breeds, a total of 100 dogs were included in the study. The dogs were offered two tablets of each of the formulations.

The results in summary were that the biscuit treats were eaten readily by most of the dogs; compared to other investigational tablets, two of the formulations containing emodepside displayed the highest acceptability; one of these formulations is that of the marketed product. The formulation proposed for marketing was more acceptable than the control product. The findings of the second phase confirmed the good acceptance of the formulation proposed for marketing with 66.67% of dogs ingesting both tablets.

OVERALL CONCLUSION ON EFFICACY

Profender spot-on solution for cats

The dose confirmation studies provided support efficacy of the final formulation against the following parasites (stages):

-Nematodes:
- *Toxocara cati* (mature adult, immature adult, L4 and L3)
- *Toxascaris leonina* (mature adult, immature adult and L4)
- *Ancylostoma tubaeforme* (mature adult, immature adult and L4)

-Cestodes:
- *Dipylidium caninum* (adult)
- *Taenia taeniaeformis* (adult)
- *Echinococcus multilocularis* (adult)

Based on the results of the field study, it is accepted that the test product is highly effective against patent nematode (*Toxocara cati*) and cestode (*Dipylidium caninum* and *Taeniidae spp*.) infections in the cat.

There is also evidence of efficacy against *Toxascaris leonina* and *Ancylostoma tubaeforme*, despite the field data relating to these two parasites being limited. The claims against the mature adult, immature adult and L4 stages of these two nematodes are justified.

It is accepted that the product is well tolerated under field conditions of use.

Profender modified-release tablets for dogs

A series of clinical efficacy studies were conducted to investigate the efficacy of the final formulation and to confirm that the absence of interactions between the two active substances. Based on the study data it is evident that, when administered (as in accordance with the SPC) at a dose of 1 mg emodepside and 5 mg praziquantel/kg, the test product is effective against the following parasites (stages):

Nematodes:
- *Toxocara canis* (adult, immature adult, L4 and L3),
- *Toxascaris leonina* (adult, immature adult and L4),
- *Ancylostoma caninum* (adult and immature adult)
- *Uncinaria stenocephala* (adult and immature adult)
- *Trichuris vulpis* (adult and immature adult).

Cestodes:
- *Dipylidium caninum*,
- *Taenia spp*.,
- *Echinococcus multilocularis* (mature adult and immature)
- *E. granulosus* (mature adult and immature)

Based on the results of the field study, it is accepted that the test product is highly effective against patent nematode (*Toxocara canis, Trichuris vulpis, Ancylostoma caninum* and *Uncinaria stenocephala*) and cestode infections in the dog. The test product was as effective as (non-inferior to) the control product. The product is well tolerated under field conditions of use.

5. BENEFIT RISK ASSESSMENT

Profender spot-on solution for cats

The product contains two active substances, a new anthelmintic substance, emodepside, and an active substance previously used against tapeworms in both veterinary and human medicines, praziquantel.

The quality data provided are satisfactory. Details of the manufacturing process are provided which demonstrate that product of the desired quality is consistently produced. The specifications are appropriate to ensure the finished product is well controlled. Stability studies performed justify the shelf life and also the in-use shelf life of the multi-dose bottle. No special storage precautions are required. The finished product complies with the current TSE-Risk assessment according to Commission Directive 1999/104/EC and Note for Guidance EMEA/410/01-Rev. 2.

Emodepside is a new active substance and has a low acute toxicity by a variety of routes. Repeat dose studies in several animal species including rats, mice, cats, dogs, rabbits, indicate abnormal clinical signs (neurological, demeanour, piloerection, etc) and adverse effects on water/feed consumption, RBC parameters, platelet numbers, liver enzymes, triglyceride concentrations and glucose levels. The liver, adrenal glands, pancreas and reproductive system were the principal target organs for toxicity. Not all changes in blood values or organ weights/morphology were reversible in the studies conducted. However, tolerance studies indicate that the problems identified above were largely absent at the level of the target species. Whilst a battery of GLP-compliant developmental toxicity studies identified adverse effects in rats and rabbits, use of the molecule in pregnant cats has not been associated with any teratogenic findings. Although no carcinogenicity data were provided, the negative results in the mutagenicity studies indicate that such studies are not required. Emodepside is non-irritating to the eyes and skin, and does not appear to be a skin sensitising agent. There was no information relating to experience in man.

Praziquantel is a well-established active whose safety profile has previously been assessed by CVMP. The molecule has a low acute and repeat-dose toxicity profile by both the oral and dermal routes. Target organs for toxicity include the liver, kidney and thyroid gland. Praziquantel does not appear to adversely affect reproductive performance, and is not teratogenic. Although occasional positive findings were detected in certain in vitro chromosomal aberration studies, clastogenic damage has not been observed in vivo. Whilst no carcinogenicity studies were performed, the long-term use of praziquantel in several species (including man) has not highlighted any such concerns. The only significant concerns raised in man relate to the potential co-mutagenic effects of praziquantel, although some studies demonstrated a protective effect against mutagenicity/carcinogenicity in various helminth diseases of man. Although praziquantel is relatively more toxic when combined with emodepside, the doses required for adverse clinical signs are well in excess of the RTD in the cat.

The most common side effects observed in the target species with the recommended dose were transient, and limited to salivation and vomiting.

The user safety of the combination product was adequately addressed. However, in section 5.12 of the SPC advice was included to try and minimise dermal or oral exposure. In particular, because of the possible risk of interference with embryo foetal development, a statement has been included to indicate that women of child bearing potential should avoid contact with, or wear disposable gloves, when administering the product.

A Phase I environmental impact assessment was performed and found to be satisfactory.

The dose determination, dose confirmation and field studies provided support efficacy of the final formulation against the following parasites (stages):

-Nematodes:
Toxocara cati (mature adult, immature adult, L4 and L3)
Toxascaris leonina (mature adult, immature adult and L4)
Ancylostoma tubaeforme (mature adult, immature adult and L4)

-Cestodes:
Dipylidium caninum (adult)
Taenia taeniaeformis (adult)
Echinococcus multilocularis (adult)

Based on the results of the field study, it is accepted that the test product is highly effective against patent nematode (*Toxocara cati*) and cestode (*Dipylidium caninum* and *Taeniidae spp*.) infections in the cat.

There is also evidence of efficacy against *Toxascaris leonina* and *Ancylostoma tubaeforme*, despite the field data relating to these two parasites being limited. The claims against the mature adult, immature adult and L4 stages of these two nematodes are justified.

It is accepted that the product is well tolerated under field conditions of use.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EEC.

Profender modified-release tablets for dogs

Profender Modified-release Tablets for Dogs is a combination product containing emodepside (nematocidal) and praziquantel (cestocidal). They are available in three strengths to cover a range of dog bodyweights. The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

The product has a broad spectrum of activity, with claimed efficacy against the common nematodes and cestodes of the dog. Emodepside is a new active substance that has not yet been authorised for use in the dog. While it is accepted that the precise mode of action of emodepside remains to be elucidated, the current state of knowledge indicates that the mechanism of action is pre-synaptic at the neuromuscular junction and involves a latrophilin-like receptor. The mode of action of praziquantel is well documented and has been satisfactorily described.

The pharmacokinetic profile of emodepside and praziquantel when administered in combination orally to dogs was characterized as part of a GLP target animal safety study. For both substances, the concentration-time profile of the mean serum concentrations indicated rapid absorption following oral administration. After reaching a peak, concentrations of both substances declined with a half-life of 1.4 to 2.5 hours. A high inter-individual variability of the pharmacokinetic variables was observed. In a study conducted to investigate the influence of food on the pharmacokinetics of emodepside and praziquantel following oral administration, it was demonstrated that maximal emodepside concentration was nearly twice as high when dogs were fed compared to when not fed. Similarly, AUC_{0-12} was markedly higher in the fed state compared to the unfed state. Effects of feeding on emodepside C_{max} and AUC_{0-12} were statistically significant. From the target animal safety studies (product administered at multiples of the recommended treatment dose), it appears that the severity of adverse effects (tremor, ataxia) is greater when dogs are fed compared to when not fed.

A series of GLP-compliant studies were performed to investigate systemic tolerance to the administration of the test product. All studies were conducted using the final formulation. The predominant adverse effects observed that were considered treatment related were neurological, in particular muscle tremor. The frequency and severity of muscle tremor tended to increase with increasing dose and was accompanied by in-coordination and behavioural changes in some dogs. Typically, such effects were transient, resolving without treatment within 8 hours. In the pivotal target animal safety study (test product administered to unfed pups), it is noted that tremor (classed as 'slight') was a common occurrence following the first administration of the test product. This is considered to be linked to the age (9-11 weeks at the time of first administration) and size of pups. For later treatments in the pivotal study and in other studies conducted, tremor was recorded infrequently in pups receiving the RTD and when it occurred was classed as slight, such that it was not possible to clearly establish whether this finding was caused by treatment. Based on the information presented, the CVMP accepts that the product is well tolerated when administered at the recommended treatment dose to fasted pups of 12 weeks and older. It is noted that the SPC includes a contraindication for use in pups less than 12 weeks old.

Based on the information provided, it is clear that the incidence and intensity of adverse effects is greater when the product is administered as an overdose (3X or 5X the RTD) to fed pups or in conjunction with feeding compared to when the product is administered to fasted pups. This effect appears to be related to the pharmacokinetic profile of emodepside in fed dogs. It is noted that the SPC includes a recommendation that the product should be administered only to fasted dogs and that food should only be given 4 hours or more after treatment. The CVMP accepts that this recommendation is appropriate. No treatment related adverse effects were recorded in the field study, in which the timing of product administration in relation to feeding was not regulated.

The product is safe for the user, and for the environment, when used as recommended, and suitable warnings and precautions are indicated in the SPC.

It is noted that emodepside is from a new class of anthelmintics with a novel mode of action. Therefore, it is considered extremely unlikely that resistance to this active substance exists. In addition, there are no reports of resistance relating to praziquantel use. Notwithstanding the lack of information to indicate resistance to either of the actives, the following standard warning statement is included in the SPC "Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class."

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EEC.