

PRODUCT PROFILE

Product names:	Econor 0.5%, 1%, 10% and 50% premixes for medicated feed
EMA Procedure Nos.:	EMA/V/C/042/01-06/0/0
Applicant company:	Novartis Animal Health GmbH Austria Biochemiestraße 10 A-6250 Kundl Austria
Active substances:	Valnemulin hydrochloride
International Non-proprietary Name:	Valnemulin hydrochloride
Pharmaceutical form:	Premix for medicated feed
Strengths:	0.5 g, 1 g, 10 g and 50 g valnemulin per 100 g
Target species:	Pigs
Presentation, packaging and package sizes:	1 kg, 2.5 kg, 5 kg and/or 25 kg low density polyethylene bags in carton boxes or aluminium lined plastic bags
Withdrawal periods:	1 day
Route of administration:	In-feed use
Product type:	Pharmaceutical
Therapeutic indication:	<u>Econor 10% and 50%:</u> The treatment and prevention of swine dysentery. The treatment of clinical signs of porcine proliferative enteropathy (ileitis). The prevention of clinical signs of porcine colonic spirochaetosis (colitis) when the disease has been diagnosed in the herd. Treatment and prevention of swine enzootic pneumonia. At the recommended dosage of 10 - 12 mg/kg bodyweight lung lesions and weight loss are reduced, but infection with <i>Mycoplasma</i> <i>hyopneumoniae</i> is not eliminated. <u>Econor 0.5% and 1%:</u> For the treatment and prevention of swine dysentery. The treatment of clinical signs of porcine proliferative enteropathy (ileitis). The prevention of clinical signs of porcine colonic spirochaetosis (colitis) when the disease has been diagnosed in the herd.

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Econor is a veterinary medicinal product containing the antibiotic valnemulin, a member of the pleuromutilin group, which also includes tiamulin. Valnemulin is a new active substance intended exclusively for veterinary use. The product was originally intended for the treatment and prevention of the following indications:

Enzootic pneumonia (causative agent *Mycoplasma hyopneumoniae*)
Swine dysentery (causative agent *Brachyspira* (formerly *Serpulina*) *hyodysenteriae*)

On 27 January 2004, the European Commission approved two type II variations adding two new indications, “treatment of clinical signs of porcine proliferative enteropathy (ileitis)” and “prevention of clinical signs of porcine colonic spirochaetosis (colitis)”.

The product is presented as four formulations, a 50% premix, a 10% premix, a 1% premix and a 0.5% premix for incorporation in finished animal feed.

The product was eligible for the centralised procedure under Part B of the Annex to Council Regulation (EEC) No 2309/93 as a veterinary medicinal product intended for use in animals and containing a new active substance, which on the date of entry into force of the Regulation, was not authorised by any Member State.

2. OVERVIEW OF PART II OF THE DOSSIER: ANALYTICAL ASPECTS

2.1 QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

The product contains (in %w/w):

<u>Active ingredient:</u>	<u>50% premix</u>	<u>10% premix</u>	<u>1% premix</u>	<u>0.5% premix</u>
Valnemulin hydrochloride (equivalent to valnemulin)	53.25 (50.0)	10.65 (10.0)	1.065 (1.0)	0.5325 (0.5)

Other substances

Hypromellose (4-6 mPa.s) and Purified Talc

0.5%, 1% and 10% premix only: Colloidal Anhydrous Silica, Isopropyl Myristate and Lactose Monohydrate.

a) Containers

All products are to be supplied in either low density polyethylene (LDPE) or aluminium foil laminate bags. The LDPE bag is enclosed within an outer secondary pack (cardboard carton) affording the necessary protection from light. No measuring device is supplied since the product is not intended for individual animal treatment.

b) Product Development Studies

The application concerns four medicated premix formulations intended for incorporation into complete feeding stuff for pigs. The product range comprises a 50% premix, which may be diluted to produce 0.5%, 1% and 10% premixes. The active ingredient valnemulin, used in the form of the hydrochloride salt, is not sufficiently stable in feed preparations unless protected and is therefore coated and a further lubricant added. The coated material is to be marketed as Econor 50% premix

(containing 50% w/w valnemulin base as 53.25% w/w valnemulin hydrochloride). Econor 0.5%, 1% and 10% premixes (containing 0.5%, 1% and 10% valnemulin, as base, respectively) are dilutions of the 50% premix with a lactose monohydrate carrier. The results of a number of formulation studies are presented and the compositions of all formulations are considered fully justified.

The four strengths show comparable dissolution characteristics, which are maintained on storage.

c) Incorporation into feed

The daily dose of Econor is to be included in the complete daily ration for the animals under treatment. Incorporation rates of less than 2 kg per tonne are recommended for the 10% and 50% presentations.

The target concentrations for use are between 25 and 200 g valnemulin/kg feed in the final feed. Satisfactory data have been supplied on the uniformity of mixing into feed for the 0.5% premix and 1% premix. However, to achieve good mixture and homogeneity of incorporation, especially when the 1% premix is incorporated at a rate less than 5 kg/tonne feed, the use of a pre-mixture is recommended for Econor 1% and 10%. Data for the 50% premix did not demonstrate adequate homogeneity when it was mixed directly into feed at the lowest dosage (25 mg valnemulin/kg feed), and the use of a pre-mixture (1 part Econor 50% to 20 parts feed ingredient) is therefore required.

The HPLC assay used in the homogeneity studies has been adequately validated by the demonstration of acceptable linearity, precision, accuracy and limit of quantification.

The Applicant has demonstrated that there is no loss of homogeneity due to physical separation of the medicated premix from the feeding stuff during transport. Shipping trials have been performed with 0.5%, 1% and 10% premixes under the conditions of road transport. Mean assay and standard deviations were unchanged after transport and it can be concluded that the homogeneity of the premixes is not affected by transportation.

The potential for dust generation of the product during use has been addressed and it has been shown that the levels of the active substance in respirable dust are minimal.

Palatability of the product has been demonstrated. Poor palatability is only apparent at higher doses and only significant at doses above those recommended. A statement in the SPC addresses this issue.

2.2 METHOD OF PREPARATION

Manufacturing formulae have been provided and are complete. The manufacture of 250 kg batches of the 50% premix and 1000 kg batches of the premixes is considered to be sufficiently described. Conventional blending procedures are employed for the premixes and for filling of the finished products.

Tests for loss on drying and particle size distribution are carried out as in-process controls. When the 50% formulation is used as an intermediate for the manufacture of the 10% and 1% formulations, the active ingredient content is measured using an HPLC method. For the finished products, the fill weights are monitored during the filling process. The sum of in-process controls presented will be adequate to ensure batches of product of the desired quality, and the Applicant has provided sufficient justification for the absence of a dissolution test as a routine in-process control. The critical steps for the manufacturing process have been identified and used to determine process validation parameters. Validation data have been provided on 3 full scale batches of the 50% premix and 3 batches each of the 1% and 10% premixes on a scale of 10% of the intended commercial batch size. The results show that the manufacturing procedure is capable of consistently producing batches of product which meet the specifications for loss on drying, particle size and, in the case of the two premixes, homogeneity. The content of degradation products remains unchanged throughout the process from that of the active substance used.

No manufacturing overages are included.

2.3 CONTROL OF STARTING MATERIALS

Active substance

This active substance, valnemulin hydrochloride, is an antibiotic of the pleuromutilin group with a chemical structure similar to tiamulin. Valnemulin hydrochloride is synthesised from pleuromutilin, and both the conditions for the synthesis and the process controls have been provided.

Pleuromutilin is routinely monitored for impurities, the main impurity being 14-acetyl mutilin. Furthermore the impurity profile of the first intermediate of the manufacturing process is closely monitored, as is the impurity profile of valnemulin. Comprehensive specifications have been provided for all the other starting and intermediate materials.

A number of analytical procedures for the determination of starting materials, reagents, solvents, impurities and degradation products have been described in the dossier. In all cases detailed data for the validation of these methods has been presented. Methods of separation, detection limits, recoveries and repeatability are in all cases satisfactory. A comprehensive discussion of the impurities and degradation products has been provided. The potential isomerism of valnemulin has been thoroughly investigated. Optical purity is checked on a routine basis by means of specific optical rotation measurement. The physico-chemical properties have been comprehensively evaluated.

No pharmacopoeial monograph is available for the active substance. An in-house specification is therefore applied to the valnemulin hydrochloride, and full details have been provided.

Satisfactory validation data have been presented for the assays of valnemulin, its related impurities and degradation products, and also for the determination of residual solvents.

Other substances

Appropriately, all the excipients, including purified water used in the coating process, are required to comply with the requirements of the relevant monographs in the European Pharmacopoeia. Monograph references and Certificates of Analysis have been provided for all the excipients.

Packaging materials

Specifications have been provided for the low density polyethylene and aluminium foil laminate bags and are considered appropriate. Assurances have been provided that these materials are approved for food contact use.

Certificates of Analysis for at least two batches of all of the starting materials are presented and show compliance with the specifications.

2.4 CONTROL AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

Not applicable.

2.5 CONTROL OF THE FINISHED PRODUCT

The release specifications have been provided. Limits for the particle size of the finished product are considered unnecessary since this parameter is controlled in-process during the manufacture of the 50% premix, and this is used to prepare the 0.5%, 1% and 10% premixes. Control of the dissolution of finished product has been shown to be unnecessary.

The tests and limits contained within the specifications are considered satisfactory for control of the finished products. The HPLC methods used for the assay of the active component and for the determination of the content of related impurities and degradation products have been soundly validated. The reference standards for the active substance and the three named related impurities and degradation products have been fully characterised.

Batch analysis data have been provided for three full scale batches of the 50% premix, and for three batches each of the 1% and 10% premixes at a scale of 10% of the intended commercial batch size. All comply with the proposed specification in all respects.

Separate Check specifications, to apply throughout the shelf-life of the product, are included. These were identical to the release specifications with the exception of the limits for assay where a lower limit of 94% label strength was agreed, and for unknown related impurities and degradation products where the content is permitted to increase by 0.5%.

2.6 STABILITY

A comprehensive discussion and detailed reports of investigations into the routes and mechanisms of degradation of the active substance have been provided. These studies have also revealed that the active substance is sensitive to both light and moisture.

Active substance

Three batches each of development, pilot and production scale material have been stability tested over 60, 36 and 6 months respectively. Testing has been carried out, at various combinations of temperature and humidity, in the commercial pack, and for the development batches, in polyethylene bags. These studies are supplemented by storage of the product at extremes of temperature, but in glass jars. The quality characteristics tested and methods used were those of the active substance specification and are considered entirely adequate to monitor relevant changes on storage. Based upon these studies it can be concluded that the active substance is very stable.

When stored protected from moisture, all quality characteristics examined remain substantially unchanged at all temperatures except 50°C. Storage under humid conditions in permeable packaging causes water uptake, changes in appearance and the formation of unidentified degradation products.

It is considered that a shelf life of 5 years is appropriate for the active substance when stored at temperatures not exceeding 30°C with protection from light and moisture. An additional warning to tightly close the container following dispensing is applied.

Finished product

The results of stability tests on five batches in total of the 50% premix as well as three batches of the 0.5% and 1% premix and six batches of the 10% premix are available.

For the chosen storage conditions no significant change was observed in any of the samples tested. Based upon the data provided the following shelf lives and storage warnings are applied:

Polyethylene bags:

Store below 25°C
Store in a dry place, protect from light.
Shelf life: 3 years

Aluminium foil laminate bags:

Store below 25°C
Shelf life: 3 years

Econor is stable during pelleting in feed under moderate conditions, under reasonably low pressure and avoiding the use of abrasive components. Preconditioning with steam and temperatures up to 75°C is considered acceptable.

Stability data have also been provided for the 50% product incorporated into a vitamin and mineral mixture (to achieve a 1.5% valnemulin content), which was then stored in paper sacks (which exclude light). Using the HPLC assay method, which has been validated for this purpose, the results support a shelf-life of 6 months at room temperature.

3. OVERVIEW OF PART III OF THE DOSSIER: TOXICOLOGICAL AND PHARMACOLOGICAL ASPECTS

3.A SAFETY

3.1 INTRODUCTION

Valnemulin is a new semi-synthetic antibiotic derived by fermentation. It acts by inhibition of protein synthesis at the level of the bacterial ribosome. It has been proposed for administration, as the hydrochloride, in the feed of pigs.

3.2 PHARMACOLOGY

See section 4.1.1

3.3 TOXICOLOGY

3.3.1 Single dose toxicity

The substance is of moderate to low acute oral toxicity.

In male and female Sprague-Dawley rats, the acute oral LD₅₀ was greater than 1000 mg/kg bodyweight but less than 2000 mg/kg bodyweight. The acute oral LD₅₀ values in mice were 1710 and 1482 mg/kg bodyweight for males and females respectively. Overt signs of toxicity included reduced activity, piloerection, ataxia, hunched appearance and laboured breathing.

3.3.2 Repeated dose toxicity

Groups of 20 to 25 Sprague-Dawley rats were fed diets calculated to provide 0, 1, 20 or 200 mg/kg bodyweight per day of the substance for 13 weeks. At termination, groups of 5/sex rats from the 0 and 200 mg/kg bodyweight group were retained on untreated diet for a further 4 weeks to check for reversibility of any effects. In the 200 mg/kg bodyweight group, body weight gain and food consumption were significantly reduced in both sexes and the mean cell haemoglobin content (MCHC) was slightly reduced. There were significant increases in gamma-glutamyl transpeptidase (GGT), aspartate transaminase (AST), alanine transaminase (ALT), blood-urea nitrogen (BUN) and potassium concentrations in males given 200 mg/kg bodyweight. At necropsy, the incidence and severity of hepatic lesions were increased in the 20 and 200 mg/kg bodyweight groups and the incidence of thyroid follicular epithelial hyperplasia was increased at 200 mg/kg bodyweight. Periportal vacuolation of the liver was also observed in the 200 mg/kg bodyweight group at the end of the recovery period. The NOEL was 1 mg/kg bodyweight per day.

A second 13-week study with no recovery phase was carried out to determine a more definitive NOEL. The rats were fed diets calculated to provide 0, 8, 16, 32 or 64 mg/kg bodyweight. Toxic effects on the liver were observed, these were very similar to those in the first study. However there were no effects on the thyroid. The NOEL was 8 mg/kg bodyweight per day.

Groups of 5/sex CD-1 mice were fed diets calculated to provide 0, 20, 100, 300 or 1000 mg/kg bodyweight per day for 4 weeks. Because of severe toxicity (emaciation, weight loss), the 1000 mg/kg bodyweight dose was reduced to 700 mg/kg bodyweight but the toxic effects continued and the group

was terminated on day 21 of the study. In the 300 mg/kg bodyweight group, body weight gain was significantly reduced, liver weights were significantly increased and there were histopathological changes in the liver. Microscopic changes attributable to treatment were also observed in the livers from mice given 20 and 100 mg/kg bodyweight. In this study no haematology, clinical chemistry or urinalysis investigations were carried out and the pathological examinations did not cover the full range of tissues. The study was designed as a range-finding study and no NOEL was established.

Groups of 4/sex Beagle dogs were given daily oral doses of 0, 10, 30 or 100 mg/kg bodyweight per day, in gelatin capsules, for 13 weeks. The doses were selected on the basis of results from a range-finding study in which doses of 120 mg/kg bodyweight and above caused reduced food consumption and weight loss. One male dog given 100 mg/kg bodyweight had severe convulsions after dosing on the 3rd day of the study and was euthanised. Body weight gain and food consumption were reduced in dogs given 100 mg/kg bodyweight and plasma alkaline phosphatase values were significantly increased in this group during weeks 6 and 12. There were some significant changes in haematology values in males (but not females) but these were not dose-related and were not consistent throughout the study; they probably represented chance findings. There were no gross- or histopathological findings attributable to treatment. The NOEL was 30 mg/kg bodyweight per day.

3.3.3 Tolerance in the target species

See section 4.1.2

3.3.4 Reproductive toxicity (including teratogenicity)

Teratogenicity studies have been conducted in rats and mice.

Groups of Sprague-Dawley rats were given daily oral doses of 0, 8, 40 or 200/160 mg/kg bodyweight throughout the breeding of 2 generations, with 2 litters per generation. Eleven days into the study, the top dose level of 200 mg/kg bodyweight was reduced to 160 mg/kg bodyweight due to severe toxicity. However signs of toxicity (convulsions preceding death in 2 male parental animals) and reduced parental body weight gain was still seen after the dose was reduced. At necropsy of the F0 and F1b adults, the incidence of liver lesions (prominent lobulation and/or pale focus) was increased in the 200 mg/kg bodyweight group compared with the controls. There were no effects on mating performance, fertility, litter size, pup weight or pup survival at any dose level. The NOEL based on parental toxicity was 40 mg/kg bodyweight per day.

Groups of 30 female CD-1 mice were given daily oral doses of 0, 10, 30 or 100 mg/kg bodyweight per day from days 6 to 15 of gestation. Two dams given 100 mg/kg bodyweight showed piloerection, hunched posture, ataxia and dull eyes. Body weight gain and food consumption were reduced at 30 and 100 mg/kg bodyweight. There was no evidence of teratogenicity at any dose level. The NOELs for foetotoxicity and maternal toxicity were 10 mg/kg bodyweight per day.

Groups of pregnant female Sprague-Dawley rats were given daily oral doses of 0, 25, 75 or 225 mg/kg bodyweight per day from days 6 to 16 of gestation. The dose of 225 mg/kg bodyweight caused both maternal toxicity and foetotoxicity (increased incidence of wavy ribs and delayed ossification). There was no evidence of teratogenicity at any dose level. The NOEL for both foetotoxicity and maternal toxicity was 75 mg/kg bodyweight per day.

The rat and mouse data suggest absence of teratogenicity but since no teratogenicity studies have been conducted in the target species, the following statement is included in section 5.6 of the SPC “Use during pregnancy and lactation”:

“Whilst studies in rats and mice have not produced any evidence of teratogenic effect, the safety in pregnant and lactating sows has not been established.”

3.3.5 Mutagenicity

No evidence of mutagenicity was observed in an *in vitro* bacterial assay for gene mutation in *S. typhimurium*, an *in vitro* assay for gene mutation in Chinese hamster ovary (CHO) cells nor in an *in vitro* UDS assay in primary rat hepatocytes. Weak positive results were obtained at toxic concentrations in the absence of metabolic activation in an *in vitro* assay in L5178Y mouse lymphoma cells; several deficiencies were noted in the study and it was concluded that a weak clastogenic effect under these conditions was meaningless. A weak clastogenic effect was observed in the presence of metabolic activation in an *in vitro* cytogenetics assay in CHO cells at toxic concentrations, but with no dose-response. In a second *in vitro* cytogenetics assay in CHO cells, negative results were again obtained in the absence of metabolic activation but an increased frequency of cells with structural chromosome aberrations was observed in the presence of S9; however, the effect was small, not reproduced between experiments and of doubtful biological significance. Evidence of DNA-binding was observed in CHO suspensions; however the design of the assay did not have the necessary power to distinguish covalent binding of the substance from artefactual increases. A well conducted *in vivo* micronucleus test gave negative results. Clear negative results were obtained in an *in vitro/in vivo* UDS assay in liver following oral doses of 800 and 2000 mg/kg bodyweight to Crl:CD rats. Overall, it was concluded that there was no good evidence for the induction of gene mutations by the test substance and that there was marginal evidence of clastogenicity *in vitro* but not *in vivo*.

3.3.6 Carcinogenicity

No data on carcinogenicity were provided but in view of the above results and the nature of the compound, it was agreed that carcinogenicity studies were not required.

3.4 STUDIES OF OTHER EFFECTS

3.4.1 Immunotoxicity

In the repeated-dose studies, no effects were observed which were indicative of an effect on the immune system.

3.4.2 Skin sensitisation

Skin sensitisation was investigated in a Magnusson & Kligman maximisation test in the guinea pig. No evidence of skin sensitisation was seen in 9 out of 10 test animals. An equivocal response was observed in the remaining animal. The Committee also noted that the related substance tiamulin causes skin sensitisation in around 2 % of exposed humans.

3.4.3 Hepatotoxicity

A toxicological ADI of 80 µg/kg bodyweight per day (i.e. 4.8 mg per person per day) was calculated by applying a safety factor of 100 to the NOEL of 8 mg/kg bodyweight per day, based on hepatotoxicity, which was established in the 13-week repeated-dose study in rats.

3.4.4 Microbiological studies

Microbiological activity of the active ingredient and its residues has also been investigated. A microbiological ADI of 477 µg per person per day was established for valnemulin. As this is lower than the toxicological ADI the overall safety assessment was based on the microbiological ADI.

3.5 OPERATOR SAFETY

Reference is also made to sections 3.4.1 and 3.4.2. of this report.

The NOEL in the 4-hour inhalation toxicity study in rats was 53 µg per litre of air. The study used the 10 % premix formulation and so the NOEL was probably equivalent to 5.3 µg/litre of valnemulin.

Higher doses caused overt signs of toxicity. Body weight gain was reduced at 258 µg product/litre and above. Studies of this type may exaggerate the apparent inhalation toxicity because the animals suffer stress from being restrained.

The Applicant has calculated the likely amount of valnemulin in the air, based on the amount administered to pigs, the stocking density for pigs in the UK and ventilation rates in UK animal houses. The result, when compared with the NOEL from the inhalation study gives a very wide “margin of safety” for operators.

Even if the likely amount of valnemulin in the air is compared with the NOEL for (oral) repeated-dose toxicity in the rat (8 mg/kg bodyweight per day, based on hepatotoxicity), there is still a very satisfactory margin of safety for operators.

The Applicant also provided details of a Stauber-Heubach test for dusting potential, for Econor 1%, 10% and 50% premixes according to Council Regulation 85/157/EEC. The results indicate a very low content of <0.3 % of flyable dust, which consists mainly of one of the inert excipients.

The Committee concluded that the product appears to be safe from an operator standpoint but that an advisory note should appear in section 5.12 of the SPC recommending that direct contact with the skin and mucous membranes should be avoided.

3.6 ECOTOXICITY

Data have been presented to show that no metabolite accounts for more than 20 % of the administered dose. Therefore, on the basis of the CVMP guidelines, only valnemulin needs to be considered. The main route of excretion of valnemulin is by the faecal route and accounts for 0.2 % of the administered dose.

Predicted Environmental Concentration (PEC) calculations for soil have been produced based on a worst case scenario of no degradation in manure and treatment of pigs of 95 kg bodyweight. The dose was assumed to be 10 mg/kg bw/day for 21 days. It was assumed that manure was ploughed to a depth of 25 cm and applied at a rate equivalent to 170 kg nitrogen/ha. This gave a PEC_{soil} under European conditions of 4.7 µg/kg. In addition, a sensitivity analysis has been conducted on the PEC calculation to investigate the effect of different assumptions, such as when manure is not ploughed into soil, when pigs of 60 kg are treated (considered a more realistic weight), and to take account of degradation during 90 days storage. The highest PEC was 34.5 µg/kg under UK conditions when manure from 95 kg pigs was not ploughed into soil and there was no degradation during storage of manure. This PEC reduced to 5.5 µg/kg when 60 kg pigs were treated and manure was stored for 60 days at 25°C.

PEC calculations have been undertaken for groundwater. Initially the simple calculation given in the CVMP guidelines was used and not unexpectedly for an extreme worst case calculation the trigger value was exceeded. A more realistic modelling approach was then used. Considering an application rate of 17683 mg/ha/year, the groundwater PECs are all below 100 ng/l, except for one case. For the Lower Greensand aquifers the PEC_{groundwater} could be up to 130 ng/l. However, this PEC_{groundwater} is based on the worst-case PEC_{soil}. With pigs of lower bodyweight and degradation of valnemulin during storage, less of the active ingredient would be spread onto land.

Additional ecotoxicity data are available for valnemulin comprising a *Daphnia magna* 48-hour EC₅₀, a 28-day toxicity study in fish, phytotoxicity data and data on microorganisms. Quantitative Structure Activity Relationships (QSARs) were used to predict toxicity to *Daphnia magna*, a fish LC₅₀, an algae EC₅₀, and an earthworm LC₅₀. Results of studies with tiamulin and predicted toxicity of tiamulin were also presented.

With the available data on the active ingredient and a related chemical it is considered that the predictions made were valid for valnemulin. Where experimental data and predictions were available these compared well. Based on these data the use of this product would not be predicted to pose a risk to the environment.

3.B RESIDUES

3.7 Metabolism and Residue Kinetics

3.7.1 Pharmacokinetic Studies

Dogs, Rats:

The pharmacokinetics of the substance ³H-labelled in the vinyl moiety was studied in Beagle dogs following oral administration at 10 and 30 mg/kg bodyweight and intravenous administration at 3 mg/kg bodyweight and in Sprague-Dawley rats following oral administration at 20 mg/kg bodyweight and intravenous administration at approx. 6 mg/kg bodyweight. In both species the substance was rapidly and completely absorbed after oral administration with bioavailability around 100 %. The substance was widely distributed to the tissues. In rats killed 3 hours after oral dosing, high concentrations were found in the lung, liver and gastrointestinal tract. Radio HPLC profiling indicated 22 different metabolites in rat plasma, liver, urine and faeces. There were considerable inter-animal variations in the amounts of the different metabolites found in the tissues. In dogs given daily oral doses of 30 mg/kg bodyweight per day for 7 days and killed 2 hours after the last dose, high concentrations were found in liver and in bile. After both oral and intravenous dosing, the substance and its metabolites were excreted, predominantly in the faeces. Excretion of expired ³H₂O was minimal. The metabolites in tissues and excreta were not identified. However comparison of the radio HPLC profiles for rats and dogs with those for pigs indicated that there were no major qualitative differences in biotransformation between the 3 species. Quantitative differences were mainly noted in the liver with unmetabolised parent compound accounting for approximately 17 % in the dog up to 16 % in pig liver and 46 % in rat liver (depending on time-point).

Pigs:

Following oral administration to pigs, valnemulin was rapidly absorbed. After a single oral dose of 10 mg/kg bodyweight of the hydrochloride, t_{max} was 1.85 hours, c_{max} was 1.29 µg/ml and area under curve (AUC) was 5.58 µg/ml per hour; these figures increased to 2.9 hours, 2.67 µg/ml and 18.23 µg/ml per hour when the dose given was 25 mg/kg bw, and 4.15 hours, 6.23 µg/ml and 67.3 µg/ml per hour when the dose given was 50 mg/kg bodyweight. Following repeated doses of 5 mg/kg bodyweight twice daily, a plateau in plasma levels had been approached by 7.5 days. No information is available on absolute bioavailability in the pig since intravenous studies have not been carried out.

Valnemulin was excreted rapidly, mostly via the bile and faeces (around 87 % of the total dose by 120 hours after the last dose when pigs were given 5 mg/kg bodyweight twice daily for 7.5 days). Excretion in urine over the same period was around 3 %.

3.7.2 Residue Depletion Studies

10 % Premix was given twice daily to 25 pigs aged approximately 14 weeks at a concentration of 100 mg/kg feed for 28 days (equivalent to a nominal dose of 5 mg valnemulin/kg bw/day) or at a concentration of 300 mg/kg feed (equivalent to a nominal dose of 15 mg valnemulin /kg bw/day). There appeared to be a palatability problem with the feed as the mean doses actually achieved were lower than expected at 3.8 and 11.6 mg/kg bw/day for the low and high doses, respectively.

Samples of muscle, liver, kidney, skin/fat and plasma were analysed for residues of valnemulin using a HPLC method. The highest residues of valnemulin were found in the livers of animals given 11.6 mg/kg bw/day: a mean residue of 455 µg/kg 8 hours after final treatment, 113 µg/kg after 1 day and below the limit of quantification (25 µg/kg) after 3 days. The mean residues in kidneys were 94 µg/kg (8 hours), 63 µg/kg (day 1), 111 µg/kg (day 2) and below the limit of quantification (25 µg/kg) at day 3. Residues of valnemulin were below the limit of quantification in skin and fat at all points in time. In muscle mean concentrations were 33 µg/kg at 8 hours withdrawal time declining below the limit of quantification (25 µg/kg) by day 3.

Residues above the limit of quantification were found in kidney samples (but not other tissues) from untreated control pigs. In addition, residues in kidney samples taken up to 2 days after the end of treatment did not demonstrate the decline, which was predicted from an examination of the pharmacokinetics. In fact the residues in kidney from pigs treated at the higher dose were of similar magnitude at the time points from 2 hours to 2 days after the end of dosing.

This pig residue depletion study had been included in the documentation for the MRL procedure for valnemulin. Analytical problems concerning residue depletion in kidneys were encountered. The validity of the results of this study was questioned by the CVMP because of the finding of an interfering peak in unmedicated control kidney samples and a withdrawal period of 4 days was set by the CVMP for the Econor products in question (50% and 10% premix).

In order to reduce the withdrawal period from 4 days to 1 day, further residue data were submitted after initial authorisation.

A new GLP-compliant study was submitted with 35 Large White hybrid pigs (approximately 3 months old) fed twice a day a diet containing Econor 10% premix at a level corresponding to 12 mg active ingredient/kg bw/day for a period of 21 consecutive days. A group of 5 pigs (3 males and 2 females) was retained as untreated controls. Since the majority of the animals became initially inappetent (considered to be due to unpalatability of the test diet) the study period was prolonged to allow a minimum of 21 consecutive days of dietary treatment. In severe cases the treatment was postponed and the animals received basal diet; the test material was then again gradually re-introduced into the diet. The achieved intake of valnemulin for all animals receiving medicated feed was 10.5 mg/kg bw/day. The test animals were killed at various times after the final administration of the medicated feed. Analysis of tissue samples was first performed by HPLC with fluorescence detection. The liver and kidney samples were also analysed using a new HPLC-MS detection assay.

Residues of valnemulin of 29 µg/kg were found in one sample of skin with fat, 2 hours after withdrawal of the medicated feed; residues in all other samples of skin with fat, and muscle, were below the limit of quantification.

Mean residues of valnemulin in kidney were 42 µg/kg 2 hours after the end of treatment i.e. below the MRL of 100 µg/kg set for kidney. Residues in all other kidney samples were below the limit of quantification.

Mean residues of valnemulin in liver depleted from 1889 µg/kg 2 hours after the end of treatment to 49 µg/kg 1 day after the end of treatment. Residues of 33 µg/kg were found in one liver sample taken 2 days after the end of treatment, but residues in all other samples were below the limit of quantification. 1 day after withdrawal of the treated feed, all of the individual values were clearly below the MRL set for liver (500 µg/kg).

Furthermore, the original kidney samples from the untreated pigs were re-analysed. All 5 original control kidney samples (stored as homogenised tissue for 30 months at –20°C) showed that residues of valnemulin in all samples were below the limit of quantification. The long storage period of the retained samples of 30 months was not considered to bias the analytical results, since studies on liver samples showed no degradation of the analyte after storage of at least 2 years at –20°C.

Further kidney samples from untreated animals originating from Austria (5 samples) and the U.K. (6 samples) showed no interfering peak in the relevant retention time region of valnemulin.

3.8 Maximum Residue Limits (MRLs)

Valnemulin is included in Annex I of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Valnemulin	Valnemulin	Porcine	50 µg/kg 500 µg/kg 100 µg/kg	Muscle Liver Kidney	

Based on these MRLs, it was calculated that the consumer intake of microbiologically active residues would represent approximately 17% of the microbiological ADI.

3.9 Withdrawal Periods

In the kidney residues depletion studies originally submitted, residues in 2 out of 4 kidney samples of pigs treated with the higher valnemulin dose (15 mg/kg bw) were above the MRL of 100 µg/kg at 2 days after the last dose. Therefore, a withdrawal period of 4 days was set for those presentations, which were indicated for the treatment of enzootic pneumonia with the higher dose, i.e. the 10% and 50% premix.

A withdrawal period of 1 day was set for the 1 % Econor premix formulation since this product is only indicated for treatment of intestinal disorders at a maximum dose level 3-4 mg/kg bw/day. In order to reduce the withdrawal period for the 10% and 50% formulations from 4 days to 1 day, the Applicant submitted in September 1999 extensions to the existing marketing authorisations for Econor 10% and 50%. New data were submitted confirming that the residues found in kidney in the original depletion study were due to an artefact. In the new residue depletion study, residues in all kidney samples were below the limit of quantification one day after the end of treatment. Residues in all samples of muscle and skin with fat were also below the limit of quantification, one day after the end of treatment.

Since the liver is the only tissue containing significant residues, the withdrawal period was based on the depletion of residues in liver. Residues in all liver samples were below the MRL (500 µg/kg) at one day after dosing. Therefore, a withdrawal period of one day was considered appropriate for all strengths.

Therefore, on 15 and 17 September 2000, the Commission granted the extension of a marketing authorisation for Econor 10% and 50% premixes with a withdrawal period of 1 day. These new presentations with the reduced withdrawal period replace the existing marketing authorisation for the original Econor 10% and 50% presentations.

3.10 Routine Analytical Methods for the Detection of Residues

An analytical method for routine monitoring has been provided which measures parent compound only. It involves liquid-liquid extraction followed by derivatisation and HPLC with fluorescence detection and quantification against an internal standard. This method is clearly described and has been adequately validated.

Residues of tiamulin and trimethoprim did not interfere in the analysis.

As part of the new residues depletion study, some further validation data were provided. These new data confirm the linearity, accuracy and precision of the method.

The Applicant provided information describing the determination of residues of valnemulin in porcine kidney and liver using a similar procedure to that in the routine analytical method, but additionally employing mass spectrometric detection.

The limit of quantification was 25 µg/kg for porcine liver and for porcine kidney.

4. OVERVIEW OF PART IV OF THE DOSSIER: CLINICAL ASPECTS

4.1 PRE-CLINICAL STUDIES

4.1.1 Pharmacology

4.1.1.1 Pharmacodynamics

The first pleuromutilin derivative developed for commercial reasons was tiamulin. Valnemulin was synthesised as part of a programme to develop further analogues which conferred superior activity to the basic pleuromutilin moiety.

Mode of action

Valnemulin acts by inhibition of protein synthesis, at the level of the bacterial ribosome. The antibiotic is bacteriostatic but bactericidal when 10 times or more than the MIC values are reached. Valnemulin is a potent inhibitor of protein synthesis in bacteria and at higher levels also suppressed RNA synthesis. Although a specific effect on *Mycoplasma* ribosomes was not demonstrated, binding to ribosomes extracted from *M. hyopneumoniae* cultures takes place, indicating a similar effect as in bacteria. There was a lack of effect on the same processes in eukaryotic cells.

Microbiological activity *in vivo*

1. General studies

Extensive MIC data were presented and covered a wide range of organisms as well as the ones relevant to this application: Gram-negative and Gram-positive bacteria, anaerobic bacteria, *Mycoplasma* and spirochaetes. Most strains tested were sensitive to valnemulin, with the exception of some Gram-negatives. In general, isolates were x4 to x50 more susceptible to valnemulin than to tiamulin. Susceptibility was remarkable for *Mycoplasma spp*, some spirochaetes, some anaerobes and *Chlamydia*.

2. Specific studies

Only the MIC data for the organisms of relevance to this application, from the general and the specific studies, are presented.

Note. *Treponema hyodysenteriae* is now known as *Brachyspira* (formerly *Serpulina*) *hyodysenteriae*.

Organism	MIC₅₀ (µg/ml)	MIC₉₀ (µg/ml)
<i>Mycoplasma hyopneumoniae</i>	approx. 0.0025	approx. 0.01
<i>Brachyspira hyodysenteriae</i>	approx. 0.2	approx. 1.0
<i>Brachyspira pilosicoli</i>	approx. 0.015	approx. 0.015
<i>Lawsonia intracellularis</i>	#	#

- MIC₅₀ and MIC₉₀ cannot be calculated but MIC reported to be <2.0µg/ml.

It should be noted that the indication for Porcine Proliferative Enteropathy, caused by *Lawsonia intracellularis*, and Porcine Colonic Spirochaetosis, caused by *Brachyspira* (formerly *Serpulina*) *pilosicoli*, were unsupported by field data and, therefore, were recommended to be omitted from the claims.

The MIC's of a variety of other bacteria involved in the diseases relevant to this application, or the organs affected, were reported:

<u>Bacteria</u>	<u>MIC</u>
<i>Campylobacter jejuni</i>	0.25-2.0 µg/ml
<i>M. flocculare</i>	0.015 µg/ml
<i>M. hyorhinis</i>	0.0312 µg/ml and 0.015-0.0125 µg/ml
<i>M. hyosynoviae</i>	0.0001-0.00025 µg/ml
<i>Chlamydia spp.</i>	0.008-0.03 µg/ml
<i>Haemophilus parasuis</i>	0.25 µg/ml
<i>Actinobacillus pleuropneumoniae</i>	0.0625 µg/ml or 0.125-4.0 µg/ml
<i>Pasteurella multocida</i>	2.0-16.0 µg/ml

All isolates were less sensitive to tiamulin than to valnemulin.

It was concluded that valnemulin possesses a high range of activity against a wide range of bacterial species, although its activity against the Enterobacteriaceae such as *E. coli* and *Salmonella* was limited. Against *Brachyspira* (formerly *Serpulina*) *hyodysenteriae* and *Mycoplasma hyopneumoniae*, its activity was unequalled by any other currently available antibiotic. It was also shown to have activity against other pathogens which may complicate swine dysentery and enzootic pneumonia.

Data provided on the bactericidal activity against *Mycoplasma* were derived from two studies conducted in the UK.

The first study indicated mycoplasmacidal activity at 2.5 x MIC concentrations. The second study indicated mycoplasmastatic activity at concentrations close to MIC but mycoplasmacidal activity was expected at higher concentrations of ≥ 10 MIC.

Although no data are available on pharmacological activity *in vivo*, one investigator found that valnemulin increased the contractility of vascular rings in isolated perfused preparations, but only at very high concentrations. These concentrations were in excess of those found at injection sites of experimental formulations and were well in excess of physiological concentrations.

4.1.1.2 Pharmacokinetics

See under 3.7.1

4.1.2 Tolerance in the target species

4.1.2.1 Tolerance studies

In a preliminary safety study Econor 10 % Premix, in the final dose form, was administered to 4 pigs (16-18.5kg) by incorporation into their diet, over 28 days. The dosage was 75 mg/kg, x6 the maximum recommended dosage. Clinical health, faecal consistency, feed consumption and body weight were recorded. In the first week the pigs were inappetent, which was considered to be due to the poor palatability of the product when present at a high concentration in feed. However the diet was being consumed by the second week.

It was concluded that the product was well tolerated in young pigs, although palatability might initially affect intake when the product was included at a high concentration in feed.

In a further study tolerance was investigated. Econor 10 % Premix, in the final dose form, was administered, by incorporation into their diet, to 3 groups of 8 pigs (4 males and 4 females) for at least 28 days. Another group of 8 pigs received unmedicated feed. The treated groups were administered dosages of 15, 45 & 75 mg/kg, representing x1, x3 & x6 the maximum recommended dosages for the maximum recommended duration of treatment. Pigs were observed clinically several times daily. Feed consumption and body weight were recorded. Faecal samples were taken for examination for occult blood on Days 4, 9, 15 and on the day of sacrifice. Blood samples were taken on the same days and examined for haematological and biochemical parameters.

As before, unpalatability resulted in some feed refusal. Target consumption was, however, achieved or nearly achieved following withdrawal of medicated feed and then gradual replacement up to the required concentration. The only clinical abnormality seen was transient yellow/brown or hard faeces in a few pigs in the higher dose groups. Overall, food consumption and weight gain were reduced in the 75 mg/kg group and the weight of some organs was lower at post-mortem than in the other groups. Levels of alkaline phosphatase and Alanine-aminotransferase (ALT) were slightly elevated in the higher dose groups. As Econor is unpalatable to many animals at very high doses, it was concluded that this unpalatability would prevent any major signs of intolerance if inadvertent high doses were to be administered.

No adverse effects were reported in any of the swine dysentery or enzootic pneumonia studies (maximum recommended dose of 15 mg/kg).

4.1.2.2 Pharmacovigilance

In 1999 and 2000, suspected adverse reactions relating to the treatment of pigs with Econor were observed in Denmark, Sweden, Finland and Ireland. These adverse reactions included lethargy, depression, erythema, oedema, pyrexia, ataxia, anorexia or pain and resulted in the death of a significant number of animals. With the exception of one report from Finland and one report from Ireland, all of these reactions occurred in Denmark and Sweden. The effects were observed for all strengths of the product authorised and throughout the recommended dosage range.

On the basis of the reported reactions and their impact on target animal safety, Denmark, Sweden and Finland suspended the use of Econor on their territories. Pursuant to Article 42 and Article 40(2) of Council Regulation (EEC) No 2309/93 of 22 July 1993, as amended, the European Commission requested on 6 September 2000 the opinion of the CVMP on measures necessary to ensure the safe and effective use of Econor. The CVMP considered the suspected adverse drug reactions and concluded that until the underlying mechanism(s) of the serious adverse reactions observed in conjunction with the use of Econor had been clarified, the safe use of the product would no longer be assured.

On 20 December 2000, the Commission suspended the marketing authorisation for Econor and the Marketing Authorisation Holder was asked to provide 3-monthly Periodic Safety Update Reports covering the world-wide use of Econor.

In September 2001, the Marketing Authorisation Holder provided new data investigating the pharmacokinetics of valnemulin (Econor) in different age groups of pigs, response to treatment in different pig breeds and different geographical regions, metabolism, as well as the effect of the concurrent use of other substances or influences in the feed such as zinc oxide, Vitamin E/selenium, *E.coli* proliferation and toxin production and the role of toxic degradants.

Published data indicate differences in the metabolic capacity regarding the cytochrome P450 isoenzymes in different pig breeds (conventional Danish pigs (Landrace x Yorkshire x Duroc) versus Göttingen minipigs). Also, it could be shown that the pig populations in Denmark and Sweden were likely to include a significantly higher proportion of pigs with a reduced ability to metabolise scatole, being deficient in the CYP2A P450 isoform. ADRs had been almost exclusively restricted to Sweden and Denmark, and those pigs with ADRs had also been found deficient in the CYP2A P450 isoform relative to those without ADRs. This could have explained the restricted geographic distribution of ADRs, as it concurred with the findings of the epidemiology survey, in which Swedish and Danish Landrace breeds were significantly more likely to be associated with ADRs than other breeds.

The CVMP considered, that adverse reactions probably occurred in a sub-population of pigs with a metabolic deficiency, while the majority of the EU population, plus the larger worldwide pig population, were unaffected by valnemulin treatment. The risk management therefore revolves around managing the risk within the sub-population in an effective manner.

The Committee acknowledged that the information provided could not fully identify the underlying causes of the adverse reactions. However, sufficient information was provided to give assurance that the product could be marketed with appropriate warnings in the SPC and product literature and additional commitments to be fulfilled by the Marketing Authorisation Holder.

On 5 December 2001, the Committee therefore concluded that it would be justified to allow the lift of the suspension for Econor if modifications would be made to the sections “Undesirable Effects” and “Special warnings for each target species” of the current SPC.

Undesirable Effects:

Medication of pigs with Econor has led to the occurrence of adverse reactions in the European Union. Of the cases reported in 1999-2000, the majority occurred in Denmark and Sweden (one case each in Finland and Ireland). In these countries, the incidence ranged from 0.03 to 1.76% of all pigs treated. On affected farms, one third of the pigs treated were affected, with a mortality of 1%. Affected pigs are pyrexia, exhibit inappetence, and in severe cases become incoordinated, ataxic and may become recumbent. A percentage of such pigs may also suffer oedema or erythema (posterior in distribution), and palpebral oedema. The reaction has been studied in controlled trials in susceptible animals. Mortality was less than 1%, but might be increased as a result of secondary infections.

In the case of an adverse reaction, immediate withdrawal of medication is recommended. Severely affected pigs should be removed to clean dry pens and given symptomatic treatment, including treatment for concurrent disease.

An epidemiological survey has indicated that there is likely to be an association between the susceptibility to adverse reactions and the Danish and Swedish Landrace breeds, and their crossbreeds thereof, especially younger pigs.

Special warnings for each target species

Adverse drug reactions have occurred following the use of Econor. Their occurrence may be principally restricted to the Scandinavian countries and appears to be mainly associated with breed mixes that include Danish and/or Swedish Landrace. Extreme care should therefore be taken in the use of Econor in pigs of Scandinavian origin especially of the Danish and Swedish Landrace breeds, and their crossbreeds thereof.

Furthermore, the Marketing Authorisation Holder was asked to provide PSURs at 3-monthly intervals, and to report results of further investigations as to the cause(s) of the adverse reactions at regular intervals. These studies should include detailed information on the changes in the metabolic capacities of pigs of different ages and breeds. Also, the Marketing Authorisation Holder was asked to encourage all users to report suspected treatment-related reactions.

Consequently, on 29 April 2002 the Commission lifted the suspension of the marketing authorisation for Econor.

4.1.3 Resistance

Two studies were presented which had investigated the resistance of *Mycoplasma hyopneumoniae*.

In the first, the MICs of valnemulin, tiamulin, tylosin, oxytetracycline and enrofloxacin were determined for two isolates of *Mycoplasma hyopneumoniae*. The results showed that neither valnemulin nor tiamulin readily developed resistance. The pre-passage MICs for valnemulin were 0.0025 µg/ml and 0.001 µg/ml. The post-passage MICs were 0.005 µg/ml and 0.0025 µg/ml, respectively. The post-passage MICs are favourable and demonstrate continued sensitivity to valnemulin. In contrast, a 20-100 fold resistance developed to enrofloxacin and at least a 200-500 fold resistance to tylosin. Oxytetracycline, however, only developed a 4-fold resistance.

In the second study, a reference strain and a field strain of *Mycoplasma hyopneumoniae*, both of which had developed resistance to tylosin, were used to redetermine the MIC for valnemulin and tiamulin. Apparent 2 fold and 5 fold increases in resistance were found to valnemulin and tiamulin respectively.

The above studies, while limited to only *Mycoplasma hyopneumoniae*, suggest that resistance is unlikely to be a problem.

The Applicant was asked to address the issue of cross resistance between tiamulin and valnemulin. The Committee agrees with the Applicant's comments that for *Mycoplasma hyopneumoniae* and *Brachyspira* (formerly *Serpulina*) *hyodysenteriae* resistance to tiamulin was uncommon. Cross resistance occurs in some cases but is neither inevitable nor predictable and that MIC values are not necessarily an infallible guide to predict efficacy.

Furthermore, the Committee concluded that the mechanism of valnemulin resistance in bacteria is unlikely to have adverse consequences for the following reasons:

1. Valnemulin's antibacterial spectrum of activity is limited. It is active against certain respiratory and enteric pathogens, but without effect on *Enterobacteriaceae*, the family in which plasmidic resistance transfer is of most concern.
2. Pleuromutilins, such as valnemulin are not used in human medicine.
3. Resistance in sensitive organisms would not appear to be a single-step process; it also develops extremely slowly, being very difficult to induce *in vitro*.
4. The metabolism of pleuromutilins appears to rely almost exclusively on cytochrome P-450-mediated oxidation. Cytochrome P-450 is not plasmid-encoded and therefore is not induced by a conventional antibiotic resistance mechanism (such as that of β -lactamase). Other mechanisms of resistance are of course possible, but were considered unlikely to occur.
5. Other studies have shown *in vivo*, that the closely related tiamulin does not induce resistance in intestinal coliforms, either to itself or to other antibacterials. After approximately 20 years extensive and worldwide usage, the prevalence of resistance to tiamulin even in the target organism is still very low, and shows little tendency to increase.

The Committee concluded therefore that the issue of resistance development and the potential consequences for man had been satisfactorily addressed.

In 2003, the Marketing Authorisation Holder applied for two additional indications, Porcine Colonic Spirochaetosis caused by *Brachyspira pilosicoli* and Porcine proliferative enteropathy caused by *L. intracellularis*.

The CVMP considered that an increase in the use of an antibiotic usually increases the possibility for resistance development and that the tendency for resistance development relates directly to the numbers of relevant bacterial species exposed to an antibiotic.

The Committee noted that although resistance of *B. pilosicoli* against valnemulin could be produced, it was not readily induced, proceeded in a stepwise fashion and chromosomal rather than plasmid-mediated. Prevalence of resistance to the related pleuromutilin, tiamulin, was extremely low and had shown no tendency to increase over the 15 years. Since then, resistance of *B. pilosicoli* to tiamulin and valnemulin has been reported, but at a very low level. It is often impossible to eliminate an organism, such as *B. pilosicoli*, and the use of an antibiotic preventatively suppresses disease. This consequently suppresses bacterial numbers and shedding and, as a further consequence, reduces the likelihood of resistance development. Management of resistance development is best achieved on the farm by managing the disease itself and reducing bacterial numbers.

Sensitivity tests for *Lawsonia* isolates, from tissues infected in the early 1980's and in the late 1990's, have shown no reduction in susceptibility. *Lawsonia* isolates from different geographical areas have similar sensitivity patterns, irrespective of the medication history. Also, no resistance of *Lawsonia intracellularis* to antimicrobials has been documented so far.

Based on the data provided by the Applicant, the CVMP concluded that it would be unlikely that the use of Econor against *L. intracellularis* or *B. pilosicoli* would contribute to an increase in antibiotic resistance.

4.1.4 Ionophore compatibility

Compatibility with ionophores is an area of concern with this group of compounds (pleuromutilins), particularly between tiamulin, narasin and monensin/salinomycin. The Applicant submitted a study investigating the effects of salinomycin and valnemulin. In one group the combined use of valnemulin hydrochloride (250 mg/kg feed) and salinomycin (75 mg/kg feed) resulted in a rise in serum ALT, AST and CPK levels on Days 9 and 15.

The compatibility of valnemulin with tiamulin and lincomycin has not been specifically addressed. Parenteral tiamulin was used, however, in conjunction with valnemulin at up to 75 mg/kg feed with no adverse effect in some of the clinical studies.

The issue of incompatibility in section 5.7 “Interaction with other medicaments and other forms of medication” of the SPC is addressed by the statement:

“Valnemulin has been shown to interact with the ionophore antibiotics such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin, during or at least 5 days before or after treatment with valnemulin. Severe growth depression, ataxia, paralysis or death may result.”

4.2 CLINICAL STUDIES

The majority of the clinical trials had been conducted in northern Europe, raising concerns that the higher temperatures and humidity in southern Europe may not have been accounted for in the clinical evaluation of the product. The Committee accepted the Applicant’s justification that the severity of the diseases listed in the indications for Econor is likely to be greatest in northern Europe so that trials conducted in the latter will have direct application for southern Europe as well.

Concern had initially been raised about the potential for discrepancy between the intended concentration of valnemulin in feed, and final intake by pigs under field conditions where feed consumption and calculation of pig weight to determine target intake may not be controlled precisely enough.

To address this issue the text of the SPC and product literature regarding the treatment of Swine dysentery and enzootic pneumonia include a statement to read:

“In older pigs, or in pigs with reduced appetite or on a restricted feed intake, inclusion levels may need to be increased to achieve target dosage.”

The SPC and product literature also include a formula for calculation of inclusion rates of Econor in feed (mg Econor/kg feed) taking into account the daily feed intake.

4.2.1 Acceptability

The Applicant investigated the issue of potential unpalatability of Econor and concluded that it is unlikely to be a problem at the recommended dosages. However, a statement in Section 5.4 of the SPC (Undesirable effects) reads:

“Valnemulin is well-accepted in feed, but administered at concentrations above 200 mg/kg feed may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding”.

In studies provided by the Applicant, no statistical difference were found in the feed consumption of pigs over a 48 hour period at valnemulin levels of 50, 100 and 200 mg/kg feed. All these studies used dry meal. There has been no formal examination of acceptance of valnemulin in wet feed or pellets, although these represent the majority of feed types in the EU. However, in the field trials medicated pellets and wet feed were found to be acceptable.

4.2.2 Clinical Data

The data from the challenge studies was almost all within limits of GLP standard criteria and some of the field studies were of GCP standard but the German studies lacked certain information, which would have been helpful. The statistics were carefully prepared and appropriate.

4.2.2.1 Treatment and prevention of swine dysentery

The Applicant's claim was for:

- i) 75 mg valnemulin/kg feed to give 3-4 mg/kg - for treatment
- ii) 25 mg valnemulin/kg feed to give 1.0-1.5 mg/kg - for prevention

Challenge studies

Three challenge studies were carried out in the UK: two for prevention, where veterinary medicines were administered from the time of challenge, and one for treatment, where veterinary medicines were administered after the challenge.

The levels of valnemulin used were 50, 75, 100 and 150 mg valnemulin/kg feed, with tiamulin 100 mg/kg feed as positive controls, and unmedicated negative controls. Medicated feed was administered for 10 days and then unmedicated feed was given for 14 days prior to slaughter. The results demonstrate that swine dysentery was eliminated from the groups medicated at 100 and 150 mg valnemulin/kg feed within 4 and 5 days respectively. *B. hyodysenteriae* was absent from these pigs at post-mortem. In addition, the daily weight gain data and clinical scores for the post-treatment period appear to confirm freedom from infection in these two groups in contrast to the tiamulin and untreated control groups. Treatment of swine dysentery with 75 mg valnemulin/kg feed therefore was regarded as successful and there were no clinical signs of disease at the end of the treatment period. However, infection (presence of spirochaetes) was identified in one animal at post-mortem examination.

Two controlled studies were submitted to evaluate prevention of disease. Medicated feed was given for 18-19 days (to slaughter) after infection. In the first study, levels of 20, 30 and 40 mg valnemulin/kg feed were given and in the second, levels of 5, 10 and 20 mg valnemulin/kg feed were given. In both studies a positive control group (tiamulin at 30 mg/kg feed) and a negative, unmedicated, control group were included.

In the first study, no clinical signs of swine dysentery were observed in the groups with 20 and 40 mg valnemulin/kg feed but disease occurred in the group given 30 mg valnemulin/kg feed. This was attributed to intercurrent disease; possibly bowel oedema; *B. hyodysenteriae* was not isolated. In this group erythema of perianal skin was observed which was considered to be due to valnemulin as it is a rare finding in cases of bowel oedema. An appropriate warning has been included in the SCP and product information.

In the second study, clinical signs of disease and infection were prevented in the groups given 10 and 20 mg valnemulin/kg feed but not in the group given 5 mg valnemulin/kg feed. It confirmed that the failure of 30 mg valnemulin/kg feed in the first study was due to intercurrent disease and that valnemulin was effective in the prevention of swine dysentery when included in feed at concentrations of 10 mg valnemulin/kg feed or more. In this study feed was analysed and the inclusion levels were found to be slightly lower than those intended. They were, however, within the expected range of concentrations achievable after mixing.

Field studies

Eight studies were conducted in the UK, Germany and Denmark; countries where conditions are considered by the Applicant to be representative of the disease situation for appropriate testing of valnemulin in the Community. There were 3 treatment studies and 5 prevention studies.

The treatment studies were intended to demonstrate that Econor was successful in effecting a cure for swine dysentery when administered at 75 mg valnemulin/kg feed in feed under farm conditions and that pigs continued to grow and convert feed normally if not re-infected.

The first cross-over study was conducted on a farm in the UK with a history of severe swine dysentery where previous medication with dimetridazole, tylosin, lincomycin and tiamulin had failed to control the disease. MIC data showed that the organism was sensitive to valnemulin. Two groups of about 40 pigs/group were studied. In week one, one group was treated and the other group left unmedicated. In week two, the groups were reversed. The study fulfilled the above criteria although disease did recur in the medicated group after 2-3 weeks. This may have resulted from re-infection, as pigs had indirect contact via common dunging passages, rather than from continued infection of the colonic mucosa.

The second study, also in the UK, used a cross-over design as above. Disease appeared in very young pigs on this farm, before they were weaned. Two groups of about 34 pigs/group were studied. The results were less satisfactory than those of the previous study in that there was a clinical response but it was not consistent. Various reasons were suggested for this; the main one being the low level of valnemulin in the feed (41-50 mg valnemulin/kg feed instead of 75 mg valnemulin/kg feed). Intercurrent infectious disease was present which would affect feed intake, intercurrent enteric disease obscured the clinical response and the hygiene was very poor on this farm.

The third study was conducted in Germany and also used a cross-over design as above. Two groups of 15 pigs/group were studied. The trial 'missed' the peak of the swine dysentery outbreak so that no pigs had to be individually treated. The only parameters recorded were weights of pigs although a general clinical assessment was made throughout the 14 day trial period. The differences in weight gain between the treated and unmedicated pigs were statistically significant. The very high weight gains were typical of those seen during the recovery phase of swine dysentery and the results suggested that Econor promoted the recovery of previously ill or subclinically infected pigs.

The prevention studies were intended to demonstrate that Econor was successful in preventing swine dysentery when administered at 25 mg valnemulin/kg feed in feed under farm conditions.

The first study was conducted in the UK, in two phases, on a farm with severe swine dysentery. In each trial 90 pigs were divided into 3 groups of 30 pigs (total of 180 pigs, 60 in each group). One group was medicated with 30 mg valnemulin/kg feed, one with 20 mg valnemulin/kg feed and one group acted as unmedicated controls. Severe swine dysentery occurred in 44/60 controls and in 4/120 treated pigs. Econor at 20 or 30 mg valnemulin/kg feed was almost effective in completely suppressing clinical signs of swine dysentery and in preventing weight loss and condition. There were statistically significant differences in performance between medicated and control pigs but control was not complete as in the challenge studies. There was a strong presumptive correlation between low inclusion rates and lack of efficacy. (In the first phase the inclusion rates were acceptable but in the second phase the inclusion rates were 16.4 and 11.8 mg valnemulin/kg feed, instead of 30 and 20 mg valnemulin/kg feed respectively).

The second trial was also conducted in the UK, being of a double blind and controlled design. A total of 208 pigs were included which were selected to be within a narrow weight range. Feed was medicated with either Econor or a placebo to give 32 mg/kg feed. The trial lasted for 6 weeks and there was moderate to severe challenge by the end of the fourth week. Findings were similar to those of the previous trial. Dysentery developed in 7/108 medicated pigs (10 cases) and 42/108 placebo treated pigs (66 cases). There were statistically significant differences in productivity and numbers of treatments required, in favour of valnemulin.

The third trial was conducted in Denmark, being also of a double blind and controlled design. A total of 96 pigs were included. Feed was medicated with either Econor or a placebo to give a target dose of 25 mg/kg feed. Final valnemulin inclusion rates were satisfactory at 24 mg/kg feed. Moderate to severe challenge occurred during the 4-week trial period. No Econor treated pigs developed dysentery or required treatment but dysentery developed in 11/48 placebo treated pigs (22 cases). Pigs treated with Econor had higher growth rates than the placebo treated controls and the differences were statistically significant.

The fourth trial was also conducted in Denmark and was similar to the above except that there were 108 pigs. Again, moderate to severe challenge occurred during the 4-week trial period. No Econor treated pigs developed dysentery or required treatment but dysentery developed in 21/54 placebo treated pigs (41 cases). Pigs treated with Econor had higher growth rates than the placebo treated controls and the differences were statistically significant. Actual inclusion rates were low, at 19-20.67 mg valnemulin/kg feed, instead of 25 mg valnemulin/kg feed.

The fifth trial was conducted in Germany. There were a total of 95 pigs, given either Econor or a placebo, applied as a top dressing to crushed barley, to give 25 mg valnemulin/kg feed. Moderate to severe challenge occurred during the 3-week trial period. 4/48 Econor treated pigs required treatment (4 cases), in the first or second day of the trial, and 20/47 placebo treated pigs (27 cases), scattered over the duration of the trial. The differences between the groups were statistically significant for both weight gains and treatments. The feed was a liquid one, which is common in many parts of the EU, and so a significant part of the dry matter of the ration was given as whey and a balancer generally mixed in prior to feeding. Formulation of the medication into the balancer is, therefore, extremely difficult and final concentrations may not have been adequately mixed. There were no data available for the final, actual concentrations.

No adverse effects were noted in any of the trials.

Clinical swine dysentery was successfully treated in the field using valnemulin at 75 mg valnemulin/kg feed in feed for at least 7 days. Valnemulin given at 25 mg/kg feed prevented the development of swine dysentery. In treatment and prevention studies, well-documented and statistically significant improvements in productivity occurred. Whilst 75 mg/kg feed did not eliminate infection, there was no requirement to disinfect at the end of periods of treatment and so re-infection could not be ruled out. There were no studies where treatment was followed by medication at the preventative level or, studies where prevention was preceded by a course of treatment, however, these programmes would probably have produced more effective results.

The studies confirmed that valnemulin at 75 mg/kg feed in feed for at least 7 days can successfully treat clinical swine dysentery in the field and that valnemulin at 25 mg/kg feed in feed prevents the development of swine dysentery. However, higher doses than 75 mg/kg feed or longer duration of treatment may be necessary for complete elimination of infection and a statement to this effect has been added to section 5.8 of the SPC. With regard to the prevention of swine dysentery, a recommendation to combine preventative medication with good management and hygiene practices has also been included in this section of the SPC.

Further on in section 5.8 of the SPC (Mixing Instructions), a statement has addressed the stability of valnemulin in pelleted feeds:

“The product has been shown to be stable to the pelleting process at temperatures of 75°C. Aggressive pelleting conditions such as temperatures in excess of 80°C, and the use of abrasive substances for pre-mixture should be avoided.”

4.2.2.2 Treatment and control of Swine Enzootic Pneumonia

Challenge studies

Four studies were carried out, using experimental challenge systems.

Three studies investigated prevention.

One study was carried out in Austria. Valnemulin was compared to two other pleuromutilins in piglets of about 10 kg bodyweight, challenged intra-tracheally with *M. hyopneumoniae* 3 days before the start of treatment. There were also groups of unmedicated, challenged pigs and unmedicated, unchallenged pigs. The ten valnemulin medicated pigs were given 200 mg valnemulin/kg feed for 10 days. Blood samples were taken for *Mycoplasma* serology. Respiratory signs noted on Day 13 were associated to infection with *M. hyopneumoniae*. The mean weight of the valnemulin group was nearest to that of the controls and no *M. hyopneumoniae* could be isolated from the lungs. However, lesions suggestive of enzootic pneumonia were present. This preliminary study showed that although valnemulin in a concentration of 200 mg/kg feed was active against *M. hyopneumoniae*, the clinical signs of enzootic pneumonia could not completely be prevented.

In a second study, six groups of pigs (six per group) were challenged with *M. hyopneumoniae* intra-nasally on 2 consecutive days. One group was given tiamulin at 10 mg/kg bodyweight, and 3 were given valnemulin at either 2.5, 5, 7.5 or 10 mg/kg bodyweight. One group were challenged but unmedicated. The pigs were medicated from the first day of challenge by stomach tube and killed on day 18.

A dose of 7.5 and 10 mg valnemulin/kg bodyweight significantly reduced lung lesion scores compared with the unmedicated controls. It was concluded that effective levels of valnemulin against enzootic pneumonia were 7.5 and 10 mg/kg bodyweight, although the productivity of the 7.5 mg/kg dosed group was poor. However, *M. hyopneumoniae* was not eliminated and other respiratory tract bacteria were present in the medicated groups.

In a third prevention study 7 groups of pigs with 6 animals in each group were challenged with *M. hyopneumoniae* intra-nasally on 2 consecutive days. Two groups were given 11.1 and 23 mg tiamulin/kg bodyweight. Four groups were given valnemulin at concentrations of 5.6, 11.2, 16.9 and 22.7 mg/kg bodyweight, corresponding to 100, 200, 300 and 400 mg/kg feed, respectively. One control group was challenged but unmedicated. Medicated feed was given twice daily from the first day of challenge and the animals were killed on day 18.

M. hyopneumoniae was not isolated at slaughter from the lungs of the groups given 300 and 400 mg valnemulin/kg feed, confirming that these levels prevented colonisation. The lung lesion scores were statistically lower in the 400 mg/kg feed group compared with the controls but small lesions were still present. Lung/body weight ratios were significantly reduced in the 200, 300 and 400 mg/kg feed groups compared with the controls. The study showed that 200 mg valnemulin/kg feed and higher reduced lung lesions, that 300 and 400 mg valnemulin/kg feed prevented colonisation with *M. hyopneumoniae* and that 400 mg valnemulin/kg feed prevented lesion formation.

The effect of treatment of Swine Enzootic Pneumonia was investigated in 6 groups of pigs with 6 animals in each group. The pigs were challenged with *M. hyopneumoniae* intra-nasally on 2 consecutive days and medication was started 7 days after challenge. One group was given tiamulin at 800 mg/kg feed and another group was given lincomycin at 220 mg/kg feed (the authorised inclusion rate). Three groups were given valnemulin at 200, 400 and 800 mg/kg feed. A control group was challenged but unmedicated. Slaughter was at day 21, that is, after 14 days medication.

Production parameters were of no value in distinguishing groups. The lung lesion scores were reduced in all the valnemulin groups compared with controls. Lung/bodyweight ratios were significantly reduced in the valnemulin groups given 400 and 800 mg/kg feed. Although *M. hyopneumoniae* was not eliminated from any group, the group given 800 mg valnemulin/kg feed had significantly less lesions compared with the controls.

In conclusion, when valnemulin was given in feed, from the day of challenge, at 200 mg/kg feed (the recommended inclusion rate), it reduced the lung lesions and their extent. It did the same when used for treatment 7 days after challenge, although *M. hyopneumoniae* was not eliminated. Levels of 300 and 400 mg/kg feed, when given from the day of challenge, could eliminate *M. hyopneumoniae* and also reduce lung lesion formation.

Field studies

Five trials were conducted, 4 in the UK and 1 in Germany. Different pharmaceutical forms were used in the first 4 of these trials, but pharmacokinetic and other studies had been carried out which showed that the different forms were bioequivalent.

The trials demonstrated that when valnemulin was used at 200ppm (10-12 mg/kg) for up to 4 weeks, reduction in lung lesions occurred under field conditions, and that these benefits were translated into reductions in clinical signs and improvements in growth rates and feed efficiency.

The first study was conducted on a commercial breeder/fattener farm where the prevalence of a high level of enzootic pneumonia, uncomplicated by secondary infection, had been established. Four pens of 15 pigs (60 pigs in total) were fed meal with valnemulin, incorporated at a rate of 400 mg valnemulin/kg feed to achieve a valnemulin dose of 7.93 - 10.1 mg/kg with a mean of 9.3 mg/kg. Four similar pens of pigs were given unmedicated feed. The trial period was 3 weeks and pigs were sent to slaughter 13 days later.

There was a small improvement in growth rate (of 5.9 %) and a reduction of lung lesions (by 13.6 %), compared with the unmedicated controls, but these were not statistically significant. *M. hyopneumoniae* was isolated from both medicated and unmedicated pigs. The interval of 13 days between last treatment and slaughter was considered too long, since new infections could occur preventing the difference obtained at the end of the medication period from being established.

The second trial was similarly designed. The presence of a moderate level of uncomplicated enzootic pneumonia had been established. Four replicates of pens of 15-19 pigs were given valnemulin at a rate of 300 mg/kg feed to achieve a dosage of about 10 mg/kg bodyweight (69 pigs), the remaining pigs were unmedicated. The trial period was 3 weeks and pigs were sent to slaughter one week after this. There was a 6 % improvement in growth rate and a statistically significant improvement in the percentage of pigs with lung lesions compared to the unmedicated controls (46.3 % versus 68.25 %). Although *M. hyopneumoniae* was not eliminated, it was concluded that treatment with valnemulin at 10 mg/kg bodyweight improved the performance of pigs and had a measurable effect on enzootic pneumonia.

Seventy-two percent of the pigs on the third trial farm had enzootic pneumonia lesions, with mean lesion scores of 8.95, before the trial. The trial was similar to the previous two but a positive control was included - lincomycin at the authorised inclusion of 220 mg/kg feed. The actual dose of valnemulin was 14.4 mg/kg. Medication was given in dry meal. Three replicates with 12 pigs/pen were used (36 pigs). The trial period was 3 weeks and pigs were sent to slaughter one week later. The growth rate in the valnemulin treated pigs was improved by 8.7 %, the feed conversion efficiency by 18.5 % and the mean lung lesion scores by 33.3 %, compared with the unmedicated controls. Pleuropneumonia lesions were present in the lungs at slaughter and the prevalence and severity of enzootic pneumonia was too low in this study to obtain statistically significant differences.

In the fourth trial, valnemulin was incorporated into pelleted feed in an inclusion rate of 280 mg/kg feed (9.3 mg valnemulin/kg bodyweight). A similar trial design was used. 62 pigs were treated with valnemulin for 3 weeks and were slaughtered 3 days later. The daily weight gain was improved by 13 %, the mean lung lesion score was reduced by 38.7 % and the number of pigs with lung lesions were reduced compared with the unmedicated controls. These results were statistically significant. There were similar improvements in the feed efficiency and a reduction in coughing, but these findings were not significant.

The final trial was conducted in Germany on a farm where enzootic pneumonia, uncomplicated by secondary infection, had been confirmed. Pen replicates were used as before and pigs given either valnemulin or a placebo for 3 weeks and then slaughtered 1 week after the end of the trial. Valnemulin was given in either wet or dry feed at 425 mg/kg feed to achieve 12.5 mg/kg bodyweight. Weight gains were reduced in the valnemulin treated pigs because of the presence of musculo-skeletal problems in 3 pigs. Mean lung lesion scores were reduced by 44 % and fewer pigs had severe lesions compared with the unmedicated controls and the differences were statistically significant.

No adverse reactions attributable to valnemulin were noted in any of these trials.
The results obtained in the challenge studies are consistent with those obtained in the field.

In summary, the use of valnemulin to treat and control enzootic pneumonia resulted in an improvement in growth rate of 6-13 %, an improvement in feed conversion efficiency and a reduction of lung lesion scores of about 40 %. The severity of lesions was also reduced. The levels at which these results were obtained varied between 425 mg/kg feed (12.5 mg/kg bodyweight) and 250 mg/kg feed (8-9 mg/kg bodyweight). Results were obtained under the most severe test conditions for enzootic pneumonia as treated and control pigs were in the same air space. With appropriate group management, all-in all-out husbandry and early treatment, none of which had been possible in these trials, far superior results could have been obtained. Intercurrent disease affected the results in 2 out of 5 trials but this was considered a multifactorial problem occurring on most conventional pig farms in the EU. All major feed types used in the EU were evaluated - meal, pellets and wet feed and the trials were considered by the Committee to be a realistic interpretation of the situation on commercial pig farms.

The distinction between 'treatment' and 'prevention' was considered difficult to apply in the field, where medication is given to a group of pigs.

The Committee concluded that valnemulin medication at a dose of approximately 10 mg/kg bodyweight, administered in feed, results in a consistent reduction in enzootic pneumonia lung lesions, and a consistent increase in weight gain. Based on the above results, the Committee accepted the following claim for swine enzootic pneumonia:

"Treatment and prevention of swine enzootic pneumonia. At the recommended dosage of 10 – 12 mg/kg bodyweight, lung lesions and weight loss are reduced, but infection with Mycoplasma hyopneumoniae is not eliminated."

In 2003, the Applicant submitted two type II variations proposing additional indications:

1. Prevention of Porcine Colonic Spirochaetosis (colitis) when the disease is diagnosed in the herd
2. Porcine Proliferative Enteropathy (PPE)

4.2.2.3 Prevention of Porcine colonic spirochaetosis

Porcine Colonic Spirochaetosis is an infection of the large intestine (caecum and colon) caused by *Brachyspira pilosicoli*. 158 *B. pilosicoli* strains isolated from 6 countries, between 1996 and 2003, were highly sensitive to valnemulin with values for MIC₅₀ of up to 0.25 µg/ml and MIC₉₀ up to 2.0 µg/ml.

B. pilosicoli is mainly in the lumen of the colon, closely associated with the mucosal brush border but it is not intracellular. Valnemulin levels in the content of the colon are, therefore, more relevant to support the dose. The Applicant provided data demonstrating that adequate concentrations of valnemulin were achieved in the colon. The CVMP therefore concluded that the proposed dose of valnemulin provided sufficient concentrations to prevent manifestation of disease.

Challenge studies

The Applicant provided data from two pivotal challenge studies.

1) The first challenge study was conducted in the US in 2001, including three animal groups: Non-challenged, non-medicated (1), challenged, non-medicated (2) and challenged, medicated with valnemulin (3). The challenge resulted in mild, transient diarrhoea and the organism was recovered in faecal and tissue samples.

Valnemulin medication significantly reduced the severity of histopathological lesions in the caecum and colon compared to the challenged, non-medicated pigs. Valnemulin medication eliminated the *B. pilosicoli* infection, based upon faecal cultures and immunohistochemical staining of tissues at necropsy. None of the valnemulin medicated pigs were positive for spirochaetes after medication was initiated. There was a significant difference between the challenged, valnemulin medicated pigs compared to challenged, non-medicated pigs.

2) Another study according to GCP was conducted in the UK in 2000, including three animal groups: Non-challenged, non-medicated (1), challenged, non-medicated (2) and challenged, medicated with valnemulin (3) at a dose of 25 mg/kg feed achieving at least 1.16 mg valnemulin/kg bw/day.

Valnemulin at a dose of 1.25 mg/kg/day protected pigs from experimental infection with *B. pilosicoli* when medication was started 2 days before exposure. Medication reduced the severity of clinical signs by 65% and excretion by 97%. Average daily weight gain and feed conversion efficiency improved by 30% and 18% respectively.

The CVMP concluded that valnemulin could prevent the clinical signs of Porcine Colonic Spirochaetosis when given at the proposed dosage. It can improve clinical scores and productivity in the majority of pigs, but did not do so in every case. It was capable of eliminating *B. pilosicoli* from the faeces of challenged pigs and of preventing the development of lesions and of colonisation of the large intestinal mucosa by the organism.

Field trial

The Applicant provided data from a GCP compliant field trial conducted in the UK in 2000 in a natural outbreak of Porcine Colonic Spirochaetosis. The trial was placebo controlled, blinded and conducted in 119 pigs using a randomised block design. Diarrhoea due to *B. pilosicoli* was known to occur on the farm in pigs between 6 and 14 weeks of age. This was confirmed from faeces samples 3 months before the trial started. Neither swine dysentery, (caused by *Brachyspira hyodysenteriae*) nor PPE (caused by *Lawsonia intracellularis*) were diagnosed.

119 pigs aged about 8 weeks from 6 pens were randomly allocated to either a valnemulin medicated (1.59 mg/kg bw/day) or unmedicated group. The trial ran for 28 days and clinical disease was present at the start of the trial, as there was diarrhoea and *B. pilosicoli* in faecal samples. Parameters included in the trial were: weight gain, feed consumption relative to body weight, feed conversion, clinical, faeces and blood/mucous scores and bacterial isolates on Day 0, on Days 1-28 (during the trial) and on Day 28 (at the end of the trial).

For samples obtained during the trial, from pigs with diarrhoea, there were significant differences between groups: Spirochaete shedding was completely suppressed in the valnemulin medicated pigs, in contrast to the placebo medicated pigs. After the first day, no valnemulin medicated pig had a positive sample, even in samples taken from pigs with diarrhoea. The clinical scores, cumulative faecal scores and cumulative blood/mucous in faeces scores were significantly lower in the valnemulin medicated pigs.

This field trial showed that valnemulin was effective in controlling clinical signs, suppressing shedding of spirochaetes and preventing the weight loss associated with *B. pilosicoli* infection, under field conditions. It confirmed that most of the results of the challenge studies could be replicated in the field regarding the clinical response. It did not, however, confirm the elimination of the organism from the large intestine.

On the data provided, the CVMP concluded that the proposed dosage regime of 1.0-1.5 mg valnemulin/kg bodyweight per day for up to 4 weeks was effective in the prevention of clinical signs of porcine spirochaetosis (colitis) when the disease is diagnosed in the herd.

4.2.2.4 Treatment of clinical signs of porcine proliferative enteropathy (ileitis)

Porcine proliferative enteropathy is an infection of the intestine caused by *L. intracellularis*, an obligate intracellular organism. *L. intracellularis* can only be grown in living cells and very few laboratories in the EU can culture it. *In vitro* studies of the organism are, therefore, relatively limited and confirmation of the presence of the agent usually relies on its identification in intestinal lesions at necropsy and the demonstration of its DNA in the lesions or faeces of infected pigs using the Polymerase Chain Reaction (PCR).

The minimum concentration of valnemulin likely to cause significant inhibition of the intracellular growth of *L. intracellularis* was calculated to be less than 2 µg/ml based on *in vitro* studies using rat enterocyte cell cultures. Also, it seems likely that macrolides, lincosamides and pleuromutilins can cause an enhanced uptake by the intracytoplasmatic *Lawsonia*, because of high cellular concentrations, and consequently inhibit the protein synthesis of *Lawsonia*.

The CVMP noted that in view of the difficulty of culture and the limited number of laboratories capable of culturing *L. intracellularis*, the data presented were considered sufficient to demonstrate the activity of valnemulin against *L. intracellularis*.

Challenge studies

Two pivotal challenge studies were conducted in the UK each using three animal groups: Non-challenged, non-medicated (1), challenged, medicated with tiamulin (2) and challenged, medicated with valnemulin at 75 or 125 mg/kg feed, i.e. 3.75 or 25 mg valnemulin/kg bw/day (3).

In the first study, three of the challenged, unmedicated pigs developed moderate to severe diarrhoea 2 weeks after challenge. None of the other pigs had diarrhoea or showed any other abnormal clinical signs. In the second study, all pigs gained significantly more weight than the challenged, unmedicated pigs and there were no differences between the challenged, valnemulin medicated pigs and the unchallenged, unmedicated pigs.

In the first challenge study, tiamulin performed better than valnemulin (administered at the proposed dose), suggesting that the dose of valnemulin was too low. In the second UK challenge study, 2 valnemulin inclusion rates were investigated with both doses performing equally well, eliminating both lesions and *L. intracellularis* itself.

Field trials

Porcine proliferative enteropathy is an insidious progressive disease. By the time clinical signs are seen in the field, intestinal lesions are advanced and chronic. These lesions are not rapidly reversible and it is difficult to demonstrate an improvement within the time course of the average trial. There does not appear to be a connection between gut lesions and clinical signs, as the latter can be significantly improved, with only small improvements in macroscopic and microscopic gut lesion scores. Also, PPE is rarely presented in isolation from other diseases and probably predisposes to secondary infection.

The Applicant presented three field studies: one from Denmark and two from the UK. All trials were performed in herds with confirmed presence of Porcine proliferative enteropathy and with no other major diseases present. *L. intracellularis* infection was confirmed by PCR testing of faeces. The animals received either medication with valnemulin (at an intended dose rate of 3.75 mg/kg bw/day) or placebo. Pigs were medicated for up to 10 days and monitored for a further 10 days.

The clinical response consisted of improvements in condition, reduction in diarrhoea and improvement in productivity. However, the treatment of pigs did not eliminate faecal shedding of *L. intracellularis* which could still be detected in faeces.

Based on the results, the CVMP concluded that valnemulin was effective in reducing the clinical signs of Porcine proliferative enteropathy, suppressing infection, controlling diarrhoea and reducing the weight loss associated with PPE. However, the Committee noted that infection with *L. intracellularis* was only suppressed, not eliminated. Therefore, the wording of the proposed new indication was amended to: 'The treatment of clinical signs of porcine proliferative enteropathy (ileitis)'.

5. RISK-BENEFIT ASSESSMENT AND CONCLUSION

Satisfactory data in respect of Part II of the dossier have been provided by the Applicant to show that the quality of the product is acceptable.

MRLs have been established for the active ingredient, valnemulin, and the residues studies provided show that after a withdrawal period of 1 day residues in all edible tissues are below the MRLs. The calculated Predicted Environmental Concentrations together with the ecotoxicity data provided indicate that the product when used in accordance with the SPC is unlikely to pose a risk to the environment.

The data submitted for the original application regarding pharmacology, tolerance in the target species and resistance were considered to be satisfactory. Valnemulin has a wide margin of safety and at higher than recommended dosages unpalatability is likely to result in reduced feed intake, thereby preventing serious overdose. Potential side effects at the recommended dosages were considered to be adequately addressed in the SPC. Resistance to valnemulin is difficult to induce and it was concluded that the mechanisms for resistance were unlikely to have adverse consequences.

The clinical data submitted for two indications, treatment and prevention of Swine Dysentery and Swine Enzootic Pneumonia were considered to be supportive, subject to modifications of the claims in the SPC, and efficacy was, therefore, considered to have been proven.

A dosage of 3-4 mg valnemulin/kg bodyweight (i.e. 75 mg/kg feed) was accepted for the treatment of Swine Dysentery, to be fed for at least 7 days. However, the following text was added: "This dose level is effective in the treatment of clinical disease, but higher dosages or longer duration of treatment may be necessary for complete elimination of infection."

The indication for Swine Enzootic Pneumonia was revised to: "*Treatment and prevention of swine enzootic pneumonia. At the recommended dosage of 10-12 mg/kg bodyweight, lung lesions and weight loss are reduced, but infection with Mycoplasma hyopneumoniae is not eliminated.*" As there was concern about the recommended dosage of 10-12 mg/kg bodyweight being achieved in pigs of different weights and different feed consumption if an inclusion rate of 200 mg/kg feed in the feed was used for all pigs, a formula was included in the SPC showing the different inclusion rates required to achieve the correct dose.

Since national regulations regarding implementation of medicated premixes in final feeds exist, an appropriate recommendation was included in the SPC and the product information: "Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds."

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded that the quality, the safety and the efficacy of the product are considered to be in accordance with the requirements of Council Directive 81/852/EEC (now Directive 2001/82/EC) and supports now the modified claims of the Applicant.

Consequently, the Committee agreed on 14 October 1998 that the product could be recommended for the granting of a Community marketing authorisation.

Post-Authorisation Evaluation

Due to a large number of serious adverse drug reactions observed in several Member States, on 20 December 2000 the Commission suspended the marketing authorisation for Econor in the European Union (see section 4.1.2.2 Pharmacovigilance of this EPAR).

New scientific data were submitted by the Marketing Authorisation Holder in September 2001 and evaluated by the Committee. The Committee considered that serious adverse reactions with sequelae observed in conjunction with the use of Econor probably occurred in a sub-population of pigs with a metabolic deficiency, while the majority of the EU population, plus the larger worldwide pig population, were unaffected by Econor treatment.

Based on the data submitted the CVMP concluded that the overall benefits outweigh the risks for Econor and recommended to the Commission to revoke the suspension of the marketing authorisation for Econor subject to changes to the product literature and further conditions as set out in section 4.1.2.2 of this EPAR. Consequently, on 29 April 2002 the Commission lifted the suspension of the marketing authorisation for Econor.

In 2004, the CVMP approved two new indications, Porcine Colonic Spirochaetosis caused by *Brachyspira pilosicoli* and Porcine proliferative enteropathy caused by *L. intracellularis*. Although the Committee considered that every increase in the use of an antibiotic would increase the possibility for resistance development, the CVMP concluded based on the data provided by the Applicant that it would be unlikely that the use of Econor against *L. intracellularis* or *B. pilosicoli* would contribute to an increase in antibiotic resistance.