The European Agency for the Evaluation of Medicinal Products

EMEA/CVMP/031/99
March 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

EUROPEAN PUBLIC ASSESSMENT REPORT

ECONOR 1%, 10% AND 50% PREMIXES

International Non-proprietary Name (INN): Valnemulin hydrochloride

ABSTRACT

On 12 March 1999 the European Commission issued a marketing authorisation valid throughout the European Union for the veterinary medicinal products Econor 1%, 10% and 50% premixes. This decision was based on the favourable Opinions and the Assessment Report adopted by the Committee of Veterinary Medicinal Products (CVMP) on 14 October 1998.

Novartis submitted the application for the granting of a marketing authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) on 6 June 1997.

Econor 1%, 10% and 50% premixes are presented as microgranules containing as the active ingredient, 1, 10 and 50 g valnemulin (as the hydrochloride) per 100 g respectively, for oral administration to pigs. Econor 1%, 10% and 50% are antibiotic premixes developed for incorporation in finished animal feed. Valnemulin, a member of the pleuromutilin group including tiamulin, is a substance intended exclusively for veterinary use. The product is indicated for the treatment and prevention of enzootic pneumonia (causative agent *Mycoplasma hyopneumoniae)* and swine dysentery (causative agent *Serpulina hydoysenteriae).*

Econor 1%, 10% and 50% premixes are supplied in 1 kg and 25 kg low density polyethylene bags in cardboard outers or aluminium lined plastic bags, and Econor 1%, additionally, in 2.5 kg size bags.

Econor was eligible for the centralised procedure under Part B of the Annex to Council Regulation (EEC) No 2309/93 as a formulation of 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.

Based on the original and complementary data of the dossier, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 81/852/EEC and supported the claims proposed by the Applicant. Consequently the Committee agreed on 14 October 1998 that the product be granted a Community Marketing Authorisation.

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MARKETING AUTHORISATION NUMBER SYSTEM
ADOPTED BY THE EUROPEAN COMMISSION

ECONOR 1%, 10% & 50% PREMIXES

EMEA application number	CVMP opinion No.	European Commission Authorisation No.	Veterinary Medicinal Product Presentation
EMEA/V/C/042/03/0/0	EMEA/CVMP/431/98	EU/2/98/010/001	1 g valnemulin base per 100 g premix for medicated feed – 1 kg LDPE bags in cardboard outers
		EU/2/98/010/002	1 g valnemulin base per 100 g premix for medicated feed – 2.5 kg LDPE bags in cardboard outers
		EU/2/98/010/003	1 g valnemulin base per 100 g premix for medicated feed – 25 kg LDPE bags in cardboard outers
		EU/2/98/010/004	1 g valnemulin base per 100 g premix for medicated feed – 1 kg aluminium lined plastic bags
		EU/2/98/010/005	1 g valnemulin base per 100 g premix for medicated feed – 2.5 kg aluminium lined plastic bags
		EU/2/98/010/006	1 g valnemulin base per 100 g premix for medicated feed – 25 kg aluminium lined plastic bags
EMEA/V/C/042/02/0/0	EMEA/CVMP/446/98	EU/2/98/010/007	10 g valnemulin base per 100 g premix for medicated feed – 1 kg LDPE bags in cardboard outers
		EU/2/98/010/008	10 g valnemulin base per 100 g premix for medicated feed – 25 kg LDPE bags in cardboard outers
		EU/2/98/010/009	10 g valnemulin base per 100 g premix for medicated feed – 1 kg aluminium lined plastic bags
		EU/2/98/010/010	10 g valnemulin base per 100 g premix for medicated feed – 25 kg aluminium lined plastic bags
EMEA/V/C/042/01/0/0	EMEA/CVMP/430/98	EU/2/98/010/011	50 g valnemulin base per 100 g premix for medicated feed – 1 kg LDPE bags in cardboard outers
		EU/2/98/010/012	50 g valnemulin base per 100 g premix for medicated feed – 25 kg LDPE bags in cardboard outers
		EU/2/98/010/013	50 g valnemulin base per 100 g premix for medicated feed – 1 kg aluminium lined plastic bags
		EU/2/98/010/014	50 g valnemulin base per 100 g premix for medicated feed – 25 kg aluminium lined plastic bags

PRODUCT PROFILE

Product names:	Econor 1%, 10% and 50% premixes
Procedure Nos.:	EMEA/V/C/042/01-03/0/0
Applicant company:	Novartis Animal Health GmbH Austria Biochemiestrasse 10 A-6250 Kundl Austria
Active substances:	Valnemulin hydrochloride
Proposed International Non-proprietary Name:	Valnemulin hydrochloride
Pharmaceutical form:	Premix for medicated feed
Strengths:	50% premix containing 50 g valnemulin base/100 g 10% premix containing 10 g valnemulin base/100 g 1% premix containing 1 g valnemulin base/100 g
Target species:	Pigs
Presentation, packaging and package sizes:	Econor 50% and 10% premixes - 1 kg and 25 kg low density polyethylene (LDPE) bags in cardboard outers or aluminium lined plastic bags. Econor 1% premix – 1 kg, 2.5 kg and 25 kg low density polyethylene (LDPE) bags in cardboard outers or aluminium lined plastic bags.
Withdrawal periods:	Econor 50% premix: 4 days Econor 10% premix: 4 days Econor 1% premix: 1 day
Route of administration:	Oral use
Product type:	Pharmaceutical
Therapeutic indication:	Treatment and prevention of swine dysentery Treatment and prevention of swine enzootic pneumonia

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PART I

BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Novartis submitted an application to the EMEA on 6 June 1997 for the granting of a Community marketing authorisation for ECONOR in accordance with Council Regulation (EEC) No 2309/93.

The application was validated on 17 June 1997.

During its meeting of October 1996, the Committee for Veterinary Medicinal Products appointed J. Ashley-Smith as Rapporteur and E. Obermayr as Co-Rapporteur for the assessment of the application. J. O'Brien subsequently took over the Rapporteurship at the July 1997 CVMP meeting.

2. Steps taken for the assessment of the product

- The company Novartis submitted an application to the EMEA on 6 June 1997 for the granting of a Community marketing authorisation for Econor in accordance with Council Regulation (EEC) No 2309/93. The application was validated on 17 June 1997.

- The centralised procedure started on 18 June 1997.

- The Rapporteur and Co-Rapporteur's assessment reports were circulated to CVMP Members on 24 August 1997 and 8 September 1997.

- The consolidated list of questions, as agreed by the CVMP during its meeting held on 14 -16 October 1997, was sent to the Applicant on 20 October 1997 and the clock stopped.

- The Applicant circulated the responses to the CVMP list of questions on 10 June 1998 at which point the time clock was restarted.

- The joint Rapporteur and Co-Rapporteur assessment report on the responses to the consolidated list of questions, the overview of the scientific data and the overall conclusions were circulated to the CVMP Members on 9 July 1998.

- The joint Rapporteur and Co-Rapporteur assessment report, the overview of the scientific data and the overall conclusions were discussed during the meeting of the Committee held on 8 – 10 September 1998. The Committee considered that some of the answers provided did not address satisfactorily the points raised in the list of questions and therefore agreed that the Applicant should be invited to provide oral explanations. The clock was stopped at day 209 on 8 September 1998.

- The Applicant provided oral explanations on several aspects of the dossier requiring clarification during the meeting of the Committee held on 13 - 15 October 1998 and the clock was restarted on 14 October 1998 at day 210.

- The CVMP, in the light of the agreed scientific standards and methods for evaluating veterinary medicinal products at the time of submission of the dossier, issued on 14 October 1998 a positive opinion for the granting of a Community marketing authorisation for Econor.

PART II

GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

II GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing authorisations and inspection status

Manufacturer of the medicinal product responsible for batch release:

Biochemie Gesellschaft MBH
Schaftenau Plant
A-6330 Schaftenau
Austria

A copy of the Manufacturing Authorisation issued in October 1995 by the Federal Ministry of Health, Sport and Consumer Protection of Austria has been presented.

2. Conditions or restrictions of supply and use

Veterinary medicinal product subject to prescription.

PART III

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 is intended for the treatment and prevention of the following indications:

Enzootic pneumonia (causative agent *Mycoplasma hyopneumoniae)*
Swine dysentery (causative agent *Serpulina hydoysenteriae)*

The product is presented as three formulations, a 50% premix, a 10% premix and a 1% 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):

Active ingredient:	50% premix	10% premix	1% premix
Valnemulin hydrochloride	53.25	10.65	1.065
(equivalent to valnemulin)	(50.0)	(10.0)	(1.0)

a) Containers

All three products are to be supplied in 1 kg and 25 kg bags with the 1% product additionally being presented in a 2.5 kg size. Two bag materials are proposed, either low density polyethylene (LDPE) or an aluminium foil laminate. 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 three 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 1% and 10% premixes. The active ingredient, SDZ PMD 296 (proposed INN: 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 1% and 10% premixes (containing 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 the three formulations are considered fully justified.

The three products show comparable dissolution characteristics, which are maintained on storage.

c) Incorporation into feed

The daily dose of all three products 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% products.

The target concentrations for use are between 25 and 400ppm active ingredient in the final feed. Satisfactory data have been supplied on the uniformity of mixing into feed, for the 1% premix at a final concentration of 25ppm and the 10% premix at a range of final concentrations between 25 and 500ppm. For the 50% premix, pre-dilution is recommended and the concentration in the final feed is to be between 150 and 400ppm. Data for the 50% premix did not demonstrate adequate homogeneity when it was mixed directly into feed at 25ppm, and the use of a pre-mixture (1 part Econor 50% to 20 parts feed ingredient) is therefore recommended.

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 both the 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 for all three products 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.

2.4 CONTROL AT INTERMEDIATE STAGES OF THE MANUFACTURING PROCESS

Not applicable.

2.5 CONTROL OF THE FINISHED PRODUCT

The release specifications for the three formulations 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 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.

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 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: 36 months

Aluminium foil laminate bags:

Store below 25°C
Shelf life: 36 months

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 75ºC 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. It has been proposed for administration, as the hydrochloride, to the feed of pigs.

3.2 PHARMACOLOGY

These studies have been assessed and are reported in section 4.1.1 of this report.

3.3 TOXICOLOGY

3.3.1 Single dose toxicity

The substance was of moderate to low acute oral toxicity. In male and female Sprague-Dawley rats, the acute oral LD_{50} was greater than 1000 mg/kg bw but less than 2000 mg/kg bw. The acute oral LD_{50} values in mice were 1710 and 1482 mg/kg bw 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 bw per day of the substance for 13 weeks. At termination, groups of 5/sex rats from the 0 and 200 mg/kg bw group were retained on untreated diet for a further 4 weeks to check for reversibility of any effects. In the 200 mg/kg bw 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 bw. At necropsy, the incidence and severity of hepatic lesions were increased in the 20 and 200 mg/kg bw groups and the incidence of thyroid follicular epithelial hyperplasia was increased at 200 mg/kg bw. Periportal vacuolation of the liver was also observed in the 200 mg/kg bw group at the end of the recovery period. The NOEL was 1 mg/kg bw 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 bw. 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 bw per day.

Groups of 5/sex CD-1 mice were fed diets calculated to provide 0, 20, 100, 300 or 1000 mg/kg bw per day for 4 weeks. Because of severe toxicity (emaciation, weight loss), the 1000 mg/kg bw dose was reduced to 700 mg/kg bw but the toxic effects continued and the group was terminated on day 21 of the study. In the 300 mg/kg bw 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 bw. 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 bw 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 bw and above caused reduced food consumption and weight loss. One male dog given 100 mg/kg bw had severe convulsions after dosing on the 3rd day of the study and was euthanased. Body weight gain and food consumption were reduced in dogs given 100 mg/kg

bw 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 bw per day.

Large White pigs were fed diets containing the equivalent of 75 mg/kg bw per day for 28 consecutive days. This was stated to be approximately 5 times the maximum proposed indicated dosage. The pigs were initially reluctant to feed due to the unpalatability of the test substance. However the pigs remained in good health, faecal consistency was unaffected and the animals gained weight normally.

3.3.3 Tolerance in the target species

These studies have been assessed and are reported in section 4.1.2 of this report.

3.3.4 Reproductive toxicity (including teratogenicity)

Groups of Sprague-Dawley rats were given daily oral doses of 0, 8, 40 or 200/160 mg/kg bw throughout the breeding of 2 generations, with 2 litters per generation. Eleven days into the study, the top dose level of 200 mg/kg bw was reduced to 160 mg/kg bw 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 bw 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 bw per day.
Groups of 30 female CD-1 mice were given daily oral doses of 0, 10, 30 or 100 mg/kg bw per day from days 6 to 15 of gestation. Two dams given 100 mg/kg bw showed piloerection, hunched posture, ataxia and dull eyes. Body weight gain and food consumption were reduced at 30 and 100 mg/kg bw. There was no evidence of teratogenicity at any dose level. The NOELs for foetotoxicity and maternal toxicity were 10 mg/kg bw per day.

In a range-finding study, 31.25 or 150 mg/kg per day of the test substance was administered to non-pregnant rabbits. Dosing was scheduled for 5 consecutive days. However, due to severe toxicity, treatment was discontinued after 3 and 4 days for the 2 groups respectively. It was concluded that the rabbit was not a suitable subject for a teratology study with the test substance and no definitive experiment was carried out.

Groups of pregnant female Sprague-Dawley rats were given daily oral doses of 0, 25, 75 or 225 mg/kg bw per day from days 6 to 16 of gestation. The dose of 225 mg/kg bw 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 bw per day.

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 bw 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 Magnussen & 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 bw 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 bw per day, based on hepatotoxicity, which was established in the 13-week repeated-dose study in rats.

3.4.5 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

The Committee has concluded that there was no evidence for the indication of gene mutations by the test substance and that there was marginal evidence of clastogenicity *in-vitro* but not *in-vivo* and therefore carcinogenicity studies were not required.

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

The NOEL in the 4-hour inhalational 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 inhalational 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 inhalational 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 bw 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 all three products 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 PECsoil 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 25ºC.

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 PECgroundwater could be up to 130 ng/l. However, this PECgroundwater is based on the worst-case PECsoil. 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 EC_{50}, a 28-day toxicity study in fish, phytoxicity data and data on microorganisms. Quantitative Structure Activity Relationships (QSARs) were used to predict toxicity to *Daphnia magna*, a fish LC_{50}, an algae EC_{50}, and an earthworm LC_{50}. 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

The pharmacokinetics of the substance ^{3}H-labelled in the vinyl moiety was studied in Beagle dogs following oral administration at 10 and 30 mg/kg bw and intravenous administration at 3 mg/kg bw and in Sprague-Dawley rats following oral administration at 20 mg/kg bw and intravenous

administration at approx. 6 mg/kg bw. 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 gastro-intestinal 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 bw 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 ^3H_2O 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 (depending on time-point) and 46 % in rat liver.

3.7.2 Residue Depletion Studies

Following oral administration to pigs, valnemulin was rapidly absorbed. After a single oral dose of 10 mg/kg bw 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.h; these figures increased to 2.9 hours, 2.67 µg/ml and 18.23 µg/ml.h when the dose given was 25 mg/kg bw, and 4.15 hours, 6.23 µg/ml and 67.3 µg/ml.h when the dose given was 50 mg/kg bw. Following repeated doses of 5 mg/kg bw 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.

Distribution of valnemulin to the tissues also occurred rapidly in pigs as demonstrated by radio-tracer methodology using valnemulin labelled with tritium in the vinyl moiety. In the main study, 15 animals were each given a dose of 5 mg/kg bw twice a day for 7.5 days by oral gavage. The greatest amounts of radioactivity were found in the liver (1 day after the final dose the mean concentration was 3650 µg equivalents/kg which represents around 92 % of the total amount found in the edible tissues) with less in the kidney (240 µg equivalents/kg at day one, representing around 6 %), very small amounts in muscle (70 µg equivalents/kg at one day one, representing around 2 %) and undetectable levels in skin and fat. The last time point was 8 days and at this stage, radioactive residues were 400 µg equivalents/kg in liver, 20 µg equivalents/kg in kidney and undetectable in muscle.

Valnemulin was also 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 bw twice daily for 7.5 days). Excretion in urine over the same period was around 3 %.

Pigs were given oral doses of 25 mg/kg bw valnemulin, twice a day, for 7.5 days and the residues in bile and in liver were characterised using various HPLC methods, LC-MS and ^{1}HNMR. Eleven metabolites were identified in bile and 6 of these were also found in liver. These represented approximately 50 % of the total residues in liver and 60 % of those in bile. All these metabolites retained the intact valnemulin skeleton and were oxidised either in the side chain or the pleuromutilin ring. No epoxides were found. Only 1 of the metabolites (accounting for 4.4 % of the metabolites identified) had antimicrobial activity and this was approximately 70 % that of valnemulin.

Six pigs were given oral gavage doses of 5 mg/kg bw ^{3}H-valnemulin, twice a day for 5 days. The pigs were killed (3 per time-point) 2 or 24 hours after the last dose. Total residues in tissues were determined by liquid scintillation counting. Residues of valnemulin were determined using the proposed routine analytical method based on HPLC with a limit of quantification of 25 µg/kg. Mean total residues in liver depleted from 19300 µg/kg at 2 hours to 4300 µg/kg at 24 hours. Valnemulin accounted for 8 % and 2 % of the total residues in liver at these time-points. Mean total residues in kidney depleted from 1000 µg/kg at 2 hours to approximately 400 µg/kg at 24 hours with valnemulin accounting for approximately 6 % of the total residues at both time-points. Although residues in some samples of muscle were below the Limit of Quantification, it was estimated that valnemulin accounted for approximately 6 % of the total residues in muscle over the time period 2 to 24 hours. Residues in samples of skin and fat were undetectable in all samples except for one (89 µg/kg).

The main residues depletion study in pigs used a nominal dose of 5 mg/kg bw/day or 15 mg/kg bw/day in the feed for 28 days. Actual doses received were approximately 3.8 and 11.6 mg/kg bw/day, respectively. Five pigs at each dose level were killed at each time point (2 hours, 8 hours, 1 day, 2 days, 3 days and 5 days). Parent compound was measured using the validated HPLC assay which has been proposed for routine monitoring. The highest levels of valnemulin were found in the liver of animals given 11.6 mg valnemulin/kg bw/day: mean of 455 µg/kg 8 hours after final treatment, 113 µg/kg 1 day after the final treatment, reducing to less than 25 µg/kg 3 days later. The equivalent levels for kidney were 94 µg/kg reducing to 63 µg/kg and to less than 25 µg/kg and for muscle 33 µg/kg reducing to 26 µg/kg and to less than 25 µg/kg. Valnemulin was undetectable in skin and fat at all time points.

Samples of pig liver from the previous study were re-analysed by different laboratories using both the HPLC method and a microbiological assay with *Micrococcus luteus* ATCC 9341 as the indicator organism. The limits of quantification and detection of the microbiological assay were 170 and 100 µg/kg respectively. The results indicated that residues of valnemulin in liver did not deteriorate when stored at -20°C for up to 30 months. The results from the HPLC assay were very similar to those obtained using the microbiological assay. It was concluded that the ratio of residues of valnemulin to total microbiological residues in liver was constant over the period 2 hours up to 1 day after the end of treatment and was approximately 85 %.

3.8 Maximum Residue Limits (MRLs)

As residues were undetectable in skin and fat at all time-points it was not necessary to establish MRLs for these tissues.

Valnemulin represents 85% of the total microbiologically active residues in porcine liver over the period 2 hours up to 1 day after the end of treatment.

Although similar data were not available for kidney and muscle, it was reasonable to assume that valnemulin would represent approximately 85% of the total microbiologically active residues in these tissues.

The Committee recommended therefore the inclusion of valnemulin in Annex I to 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.

Based on a ratio of 6% for the value of marker to total residues for all tissues, it was calculated that the consumer intake of total residues, based on these MRLs, would represent 24% of the toxicological ADI of 4800 µg/person/day.

3.9 Withdrawal Periods

Based on the residues depletion data for liver, and using the statistical method, the Applicant proposed withdrawal periods of 24 hours for the 10-12 mg/kg bw dose and 8 hours for the 4 mg/kg bw dose. The calculation based on residue depletion data for liver following administration of the higher dose (i.e. nominal dose of 15 mg/kg bw per day for 28 days) enabled the Committee to conclude that an overall 24-hour (one day) withdrawal period is justified.

Following administration at the nominal dose level of 15 mg/kg bw per day for 28 days, residues in 2 out of 4 kidney samples were above the MRL of 100 µg/kg at 2 days after the last dose, although the Applicant claimed that these results were spurious. Residues in all 4 kidney samples were below the Limit of Quantification (25 µg/kg) 3 days after the last dose. Therefore, a withdrawal period of at least 3 days is supported by the kidney data.

Unfortunately the kidney data were not amenable to analysis using the method described in the CVMP Note for Guidance: "Approach towards Harmonisation of Withdrawal Periods". A subsequent analysis was based on 5 time points (2 & 8 hours, 1, 2 and 3 days) and values of 12.5 µg/kg for the values which were below the LOQ of 25 µg/kg.

The CVMP, having considered all the evidence presented above, recommended a withdrawal period of 4 days, which was based on the time taken for residues in kidney samples to deplete below the MRL plus one extra day.

For the treatment of intestinal disorders where a maximum dose of 3-4mg/kg bw/day is indicated, the CVMP recommended a withdrawal period of 1 day.

Two different withdrawal periods for one formulation of product were considered by the CVMP to be impractical and confusing. Therefore, for both the 10 % premix and the 50 % granules a uniform withdrawal period of 4 days for all indications and doses was proposed.

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 (the target dose for the treatment of swine enzootic pneumonia using the 10 % premix and the 50 % granules is 10-12 mg/kg bw/day).

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. The limit of quantification was 23 µg/kg for all edible porcine tissues. Residues of tiamulin and trimethoprim did not interfere in the analysis.

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 affecting protein synthesis, in particular the ribosome factor of the system. The antibiotic is claimed to be 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 *Serpulina hyodysenteriae*.

Organism	***MIC_{50} (μg/ml)***	***MIC_{90} (μg/ml)***
Mycoplasma hyopneumoniae	*approx. 0.0025*	*approx. 0.01*
Serpulina hyodysenteriae	*approx. 0.2*	*approx. 1.0*
Serpulina pilosicoli	*approx. 0.015*	*approx. 0.015*
Lawsonia intracellularis	#	#

- MIC_{50} and MIC_{90} 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 *Serpulina pilosicoli*, are 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:

Bacteria	MIC
Campylobacter jejuni	0.25-2.0µg/ml
M. flocculare	0.015µg/ml
M. hyorhinus	0.0312µg/ml & 0.015-0.0125µg/ml
M. hyosynoviae	0.0001-0.00025µg/ml
Chlamydia spp.	0.008-0.03µg/ml
Haemophilus parasuis	0.25µg/ml
Actinobacillus pleuropneumoniae	0.0625µg/ml or 0.125-4.0µg/ml
Pasteurella multocida	2.0-16.0µg/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 more limited. Against *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 *Mycloplasma* 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 ≥10MIC.

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. The principle pharmacological effects of valnemulin are assessed in Part 3 of this report - Safety.

4.1.1.2 Pharmacokinetics

See under 3.7.1

4.1.2 Tolerance in the target species

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 inappetant, 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. Various tissues were taken, weighed and preserved.

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 were lower at post-mortem than in the other groups. Levels of alkaline phosphatase and glutamic-pyruvate transaminase were slightly elevated in the higher dose groups. As Econor is unpalatable to many animals at very high doses, this unpalatability should prevent any major signs of intolerance if inadvertent high doses were to be administered.

The maximum recommended dose of 15 mg/kg had no adverse effects on pigs.

Teratogenicity studies have only been conducted in rats and mice. These are addressed in Part 3 - Safety. It is noted that none of the field trials in the dossier included pregnant sows, nor was there a formal safety study in pregnant sows or breeding pigs, furthermore only the 2-generation study in the rat addressed the problem of the effects of valnemulin in early pregnancy (conception and the early embryo prior to implantation). The rat and mouse data suggested absence of teratogenicity in the pig but did not provide direct evidence, so that 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."*

No adverse effects were reported in any of the swine dysentery or enzootic pneumonia studies. Although it was not specifically mentioned, it is assumed that there were none in the porcine proliferative enteropathy (PPE) studies.

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 two highest concentrations of drug containing broth that showed an indicator colour change were repeatedly passaged up to ten times. The results showed that neither valnemulin nor tiamulin readily developed resistance. The pre-passage MICs for valnemulin were 0.0025 and 0.001 µg/ml. The post-passage MICs were 0.005 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 filed 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 *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.

In the case of *Lawsonia intracellularis* and *Serpulina pilosicoli*, no data were available. It should be noted that the indications for Porcine Proliferative Enteropathy, caused by *Lawsonia intracellularis*, and Porcine Colonic Spirochaetosis, caused by *S. pilosicoli*, are unsupported by field data and, therefore, recommended to be omitted from the claims.

The Applicant has reported that it would be difficult to study the mechanism of resistance when it has been so difficult to induce. 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 extremely active against certain respiratory and enteric pathogens, but without effect on *Enterobacteriaceae,* the family in which plasmidic resistance transfer is of most concern. Plasmidic transfer is more likely between related species, Baron, S. (Ed.) (1996), Medical Microbiology, 4th Edition, University of Texas.

2. Valnemulin, like tiamulin, is not used in human medicine. Nor is any member of this class of antimicrobials. Human gut flora will thus not be exposed to valnemulin from any other source.

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. (Schuster, I., Fleschurtz, C. and Helm, I. (1975), Eur. J. Biochem. 51, 571-519). Cytochrome P-450 is not plasmid-encoded and therefore is not induced by a conventional antibiotic resistance mechanism (such as that of β-lactamase - Jacobs, G.A. (1994), Trends Micro. 2, 357-360).

   Other mechanisms of resistance are of course possible, for instance the induction of a protein which protects the ribosome from attack by specific antibiotics, or specific inactivating protein binding (such as that which confers resistance to some penicillins). However such proteins might possibly cross-react with the structurally analogous tiamulin, which would however be unlikely, since tiamulin resistance is so rare in any case.

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.

6. 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.

4.1.4 Ionophore compatibility

Compatibility with ionophores is an area of concern with this group of compounds (pleuromutilins), particularly between tiamulin and monensin/salinomycin. The dossier addressed these issues. In one study, healthy pigs receiving a dry meal diet, were fed rations containing:

- basal diet only.
- salinomycin 75ppm.
- salinomycin 75ppm then valnemulin hydrochloride 31ppm + salinomycin 75ppm.
- salinomycin 75ppm then valnemulin hydrochloride 94ppm + salinomycin 75ppm.
- salinomycin 75ppm then valnemulin hydrochloride 250ppm + salinomycin 75ppm.
- valnemulin hydrochloride 250ppm.
- salinomycin 75ppm then, after a washout period, valnemulin hydrochloride 250ppm.

Animals with severe swine dysentery that are inappetant require parenteral treatment. The most commonly used products, either parenterally or via water medication, are tiamulin and lincomycin. 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 75ppm with no adverse effect when similar circumstances developed in 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 (section 5.8) and labels (section 9) 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 labels also include (in the same sections) the recommended dose of (mg/kg bodyweight) and a formula for calculation of inclusion rate in feed (mg valnemulin base/kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)).

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 200ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding".*

4.2.1 Acceptability

Studies carried out by Laber (1989), found no statistical difference in the feed consumption of pigs over a 48 hour period at valnemulin levels of 50, 100 and 200ppm. 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.

Treatment and prevention of swine dysentery

The Applicant's claim was for:
i) 75ppm to give 3-4 mg/kg - for treatment
ii) 25ppm 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 & 150ppm, with tiamulin 100ppm 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. All pigs in the unmedicated group had to be euthanased within 5 days of disease onset. The results demonstrate that swine dysentery was eliminated from the groups medicated at 100pm and 150ppm within 4 and 5 days respectively. *S. hyodysenteriae* was absent from these pigs at post-mortem. In addition, the daily liveweight 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. Swine dysentery therefore was treated successfully with 75ppm 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. In conclusion the Applicant claimed that "The new compound at levels ranging from 75-150ppm was successful in treating swine dysentery and eliminating clinical signs. Levels from 100-150ppm were successful in eliminating infection."

The two studies to evaluate prevention of disease consisted of a primary controlled study and a comparative controlled study which acted as a partial replicate, supplemented the first and improved the interpretation of results. Medicated feed was given for 18-19 days (to slaughter) after infection. In the first study, levels of 20, 30 & 40ppm were given and in the second, levels of 5, 10 & 20ppm were given. In both there was a positive control group (tiamulin at 30ppm) and a negative, unmedicated, control group.

In the first study, there was complete prevention of swine dysentery at 20 and 40ppm but disease occurred in the group given 30ppm. This was attributed to intercurrent disease; possibly bowel oedema; *S. hyodysenteriae* was isolated. The depression of feed intake was considered responsible for the breakdown. In this group erythema of perianal skin was observed which the expert considered to be due to valnemulin as it is a rare finding in cases of bowel oedema.

In the second study, disease and infection were prevented in the groups given 10 & 20ppm but not in the group given 5ppm. It confirmed that the failure of 30ppm 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 10ppm 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.

The challenge studies demonstrated that:

- Clinical swine dysentery could be treated with valnemulin hydrochloride at 75ppm in feed but 100ppm was required to eliminate the causal organism.

- Prevention was achieved with levels of as low as 10ppm.

- Intercurrent disease could interrupt preventative treatment.

- Reactions to valnemulin may occur; perianal erythema was noted in one study.

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 75ppm in feed under farm conditions and that pigs continued to grow and convert feed normally if not reinfected.

The first 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 pigs with ~ 40 in each were studied. In week one, one group was treated and the other group left unmedicated. In week two, the groups were reversed (i.e. it was a cross-over study). 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 pigs with ~ 34 in each 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 (41-50ppm instead of 75ppm). Intercurrent disease such as meningitis was present which would affect feed intake, and hence the outcome in affected animals, 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 pigs with 15 in each 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 25ppm 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 with 30 in each (total of 180 pigs, 60 in each group). One group was medicated with valnemulin 30ppm, one with valnemulin 20ppm and one group acted as unmedicated controls. Severe swine dysentery occurred in 44/60 controls and in 4/120 treated pigs. Econor at 20ppm or 30ppm 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 16.4ppm and 11.8ppm, instead of 30ppm and 20ppm 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 32ppm. 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 25ppm. Final valnemulin inclusion rates were satisfactory at 24ppm. 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 (41cases). 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 19-20.67ppm, instead of 25ppm.

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 25ppm. 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 75ppm in feed for at least 7 days. Valnemulin given at 25ppm prevented the development of swine dysentery. In treatment and prevention studies, well-documented and statistically significant improvements in productivity occurred. Whilst 75ppm did not eliminate infection, there was no requirement to disinfect at the end of periods of treatment and so reinfection 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 75ppm in feed for at least 7 days can successfully treat clinical swine dysentery in the field and that valnemulin at 25ppm in feed prevents the development of swine dysentery. However, higher doses than 75ppm 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."*

Treatment and prevention of Porcine Colonic Spirochaetosis (PCS)

The Applicant's claim was for:
i) 75ppm to give 3-4 mg/kg - for treatment
ii) 25ppm to give 1.0-1.5 mg/kg - for control

In the absence of formal clinical trial data, the Committee were not able to approve the indication.

Treatment and control of Porcine Proliferative Enteropathy (PPE)

This is also known as Porcine Intestinal Adenopathy (PIA) or, Ileitis.

The Applicant's claim was for:
i) 75ppm to give 3-4 mg/kg - for treatment
ii) 37.5ppm to give 1.5-2.0 mg/kg - for control

Although the Applicant submitted evidence that valnemulin will be effective against Porcine Proliferative Enteropathy, caused by *Lawsonia intracellularis*, no field trials were conducted to support the indication. The Committee were therefore not able to approve the indication.

Treatment and control of Swine Enzootic Pneumonia

Challenge studies

Four studies were carried out, using experimental challenge systems.

Three studies investigated prevention.

The earliest study was carried out in Austria. Two pleuromutilin antibiotics, one of which was valnemulin, were compared with tiamulin in piglets of ~10kg, challenged intra-tracheally 3 days before the start of treatment. There were also groups of unmedicated, challenged pigs and unmedicated, unchallenged pigs. The 10 valnemulin medicated pigs were given 200ppm for 10 days. Blood samples were taken for *Mycoplasma* serology. 8/10 pigs had seroconverted by Day 26 which confirmed that the respiratory signs noted on Day 13 were associated 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. Lesions suggestive of enzootic pneumonia were present. This preliminary study, according to the Applicant, suggested that valnemulin was active against *M. Hyopneumoniae, in vivo,* when given at 200ppm in feed, but that enzootic pneumonia was not completely eliminated. Valnemulin was considered to have performed better than the two comparator products.

In a second study, pigs were challenged intra-nasally on 2 consecutive days, medicated from the first day of challenge by stomach tube and killed on day 18. There were 6 groups of pigs with 6 in each. One group was given tiamulin at 10 mg/kg, and 3 were given valnemulin at either 2.5, 5, 7.5 or 10 mg/kg. One group were challenged but unmedicated. 7.5 and 10 mg/kg doses significantly reduced lung lesion scores compared with the unmedicated controls. In the 10 mg/kg dose group the lung/bodyweight ratio was also significantly lower in the 10 mg/kg dosed group compared with the unmedicated controls. It was concluded that the most effective levels of valnemulin against enzootic pneumonia were 7.5 and 10 mg/kg, although the productivity of the 7.5 mg/kg dosed group was poor. *M. hyopneumonia* was not eliminated and other respiratory tract bacteria were present in the medicated groups.

In the prevention study pigs were challenged intra-nasally on 2 consecutive days, medicated from the first day of challenge and killed on day 18 but medication was administered in feed twice daily. There were 7 groups of pigs with 6 in each. Two groups were given tiamulin at 11.1 and 23 mg/kg. Four groups were given valnemulin at 5.6, 11.2, 16.9 and 22.7 mg/kg, corresponding to 100, 200, 300 and 400ppm respectively. One group was challenged but unmedicated. *M. hyopneumoniae* was not isolated at slaughter from the lungs of the groups given 300 and 400ppm, confirming that these levels prevented colonisation. The lung lesion scores were statistically lower in the 400ppm group

compared with the controls but small lesions were still present. Lung/body weight ratios were significantly reduced in the 200, 300 and 400ppm groups compared with the controls. The study showed that 200ppm and higher reduced lung lesions, 300 and 400ppm prevented colonisation with *M. hyopneumoniae* and that 400ppm virtually prevented lesion formation.

One study investigated treatment.

This study was similar to the above but medication was started 7 days after challenge. Slaughter was at day 21, that is, after 14 days medication. There were 6 groups of pigs with 6 in each. One group was given tiamulin at 800ppm and one lincomycin at 220ppm (the authorised inclusion rate). Three groups were given valnemulin at 200, 400 and 800ppm. One group was challenged but unmedicated. 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 800ppm. Although *M. hyopneumoniae* was not eliminated from any group, the group given 800ppm valnemulin had significantly less lesions compared with the controls.

In conclusion, when valnemulin was given in feed, from the day of challenge, at 200ppm (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 400ppm, when given from the day of challenge, could eliminate *M. hyopneumoniae* and also produce a more marked reduction in lesion score.

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 ~400ppm to give ~10 mg/kg. The actual valnemulin dose was in the range 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 after this. This interval is considered too long, since new infections can occur and prevent the difference obtained at the end of the medication period from being established. There was a small improvement in growth rate (of 5.9 %) and lung lesions were reduced (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 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 300ppm to give ~10 mg/kg (69 pigs) and the rest were unmedicated. The actual dose of valnemulin was 10.6 mg/kg. 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 lung lesion scores were reduced by 42.6 % compared with the unmedicated controls. There was a statistically significant improvement in the percentage of pigs with lung lesions compared to the unmedicated controls (46.3 % versus 68.25 %). It was clear that treatment with valnemulin at 10 mg/kg 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 220ppm. 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 after this. 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 and the actual inclusion/dose was 280ppm/9.3 mg/kg. A similar trial design was used. 62/63 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 (27/28 pigs) 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 425ppm to give 12.5 mg/kg (nominal). 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.

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 ~40 %. The severity of lesions was also reduced. The levels at which these results were obtained varied between 425ppm (12.5 mg/kg) and 250ppm (8-9 mg/kg). 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 2/5 trials but this will always be a problem where multifactorial situations exist, as they do 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’ could be considered difficult to apply in the field, where medication is given to a group of pigs. Some of these will be uninfected (or at least without lung lesions), some will be acutely or chronically infected, and some will be convalescent. It is not possible to accurately predict the status of individual pigs within a group.

The results obtained in the challenge studies are consistent with those obtained in the field.

It may be 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.”*

Conclusions on clinical efficacy can be summarised as follows:

a) Swine Dysentery

- Challenge studies indicated that 75ppm valnemulin was successful in treating swine dysentery and eliminating clinical signs, but that levels of ≥100ppm were needed to eliminate infection.

- Taking into consideration the problems encountered in the field trials, typical of commercial pig farms, 75ppm valnemulin was successful in treating swine dysentery.

- The challenge studies indicated that swine dysentery could be prevented with ≥10ppm valnemulin.

- Taking into consideration the problems encountered in the field trials, typical of commercial pig farms, 25ppm valnemulin was successful in preventing swine dysentery.

b) Porcine Colonic Spirochaetosis (PCS)

- In the absence of formal clinical trial data, the Committee were not able to approve the indication.

c) Porcine Proliferative Enteropathy (PPE)

- In the absence of formal clinical trial data, the Committee were not able to approve the indication.

d) Swine Enzootic Pneumonia

- Challenge studies investigating prevention indicated that 200ppm valnemulin reduced lung lesions and their extent but *M. hyopneumoniae* was not eliminated. Levels of 300 and 400ppm prevented colonisation of *M. hyopneumoniae* and 400ppm virtually prevented lesion formation.

- Taking into consideration the severe test of the product in the field trials, as treated and control pigs were in the same air space, the field studies indicated that 200ppm valnemulin could be used to treat and control enzootic pneumonia.

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 4 days for the 50% and 10 % products and 1 day for the 1 % product, 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 pre-clinical data submitted on 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. Any potential side effects at the recommended dosages were considered to be minor and 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, 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. The clinical data for the other two proposed indications, Porcine Colonic Spirochaetosis and Porcine Proliferative Enteropathy, were not considered to be sufficiently supportive and they were not approved by the CVMP and were deleted from the SPC. Various modifications were made to the two remaining claims for Swine Dysentery and Swine Enzootic Pneumonia.

In the indication for Swine Dysentery the word "prevention" has been substituted for "control". The dosage of 3-4 mg/kg (75 ppm) was accepted for the treatment of Swine Dysentery, to be fed for at least 7 days and up to 4 weeks, but the with the following text 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 being achieved in pigs of different weights and different feed consumptions if an inclusion rate of 200 ppm 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.

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 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.

PART IV

CVMP OPINION

OPINION OF THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS ON THE GRANTING OF A MARKETING AUTHORISATION FOR

Veterinary medicinal product

Name:	Econor
International non-proprietary name:	Valnemulin hydrochloride
Pharmaceutical form:	Premix for medicated feed
Strength:	50 g valnemulin base per 100 g
Target species:	Pigs
Route of administration:	Oral administration
Withdrawal period:	4 days
Packaging and package sizes:	1 kg and 25 kg low density polyethylene bags packed in cardboard outers, or 1 kg and 25 kg aluminium lined plastic bags

Basis for opinion

Pursuant to Article 28 of Council Regulation (EEC) No 2309/93 of 22 July 1993, Novartis Animal Health GmbH Austria submitted to the EMEA on 6 June 1997 an application for a Marketing Authorisation for the above mentioned veterinary medicinal product which falls within the scope of Part B of the annex to Council Regulation (EEC) No 2309/93.

Written explanations were provided by the applicant on 11 June 1998.
Oral explanations were given by the applicant on 13 October 1998.

Opinion

1. The CVMP, having considered the application in accordance with Article 29 of Council Regulation (EEC) No 2309/93 of 22 July 1993, as set out in the appended assessment report, recommends the granting of a Marketing Authorisation for the above mentioned veterinary medicinal product for which the draft Summary of Product Characteristics is set out in Annex I.

2. **The Manufacturing Authorisation Holder responsible for batch release and the conditions of the Marketing Authorisation are set out in Annex II.**

3. The draft texts for Labelling and Package Insert are set out in Annex III.

This opinion is forwarded to the European Commission, to Member States and to the applicant, together with its annexes and appendices.

London, 14 October 1998

On behalf of the CVMP
Prof. R. Kroker, Chairman

OPINION OF THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS ON THE GRANTING OF A MARKETING AUTHORISATION FOR

Veterinary medicinal product

Name:	Econor
International non-proprietary name:	Valnemulin hydrochloride
Pharmaceutical form:	Premix for medicated feed
Strength:	10 g valnemulin base per 100 g
Target species:	Pigs
Route of administration:	Oral administration
Withdrawal period:	4 days
Packaging and package sizes:	1 kg and 25 kg low density polyethylene bags packed in cardboard outers, or 1 kg and 25 kg aluminium lined plastic bags

Basis for opinion

Pursuant to Article 28 of Council Regulation (EEC) No 2309/93 of 22 July 1993, Novartis Animal Health GmbH Austria submitted to the EMEA on 6 June 1997 an application for a Marketing Authorisation for the above mentioned veterinary medicinal product which falls within the scope of Part B of the annex to Council Regulation (EEC) No 2309/93.

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London, 14 October 1998

On behalf of the CVMP
Prof. R. Kroker, Chairman

CVMP/431/98-EN-**FINAL**
EMEA/V/C/0042/03/00/00

OPINION OF THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS ON THE GRANTING OF A MARKETING AUTHORISATION FOR

Veterinary medicinal product

Name:	Econor
International non-proprietary name:	Valnemulin hydrochloride
Pharmaceutical form:	Premix for medicated feed
Strength:	1 g valnemulin base per 100 g
Target species:	Pigs
Route of administration:	Oral administration
Withdrawal period:	1 day
Packaging and package sizes:	1 kg, 2.5 kg and 25 kg low density polyethylene bags packed in cardboard outers, or 1 kg, 2.5 kg and 25 kg aluminium lined plastic bags

Basis for opinion

Pursuant to Article 28 of Council Regulation (EEC) No 2309/93 of 22 July 1993, Novartis Animal Health GmbH Austria submitted to the EMEA on 6 June 1997 an application for a Marketing Authorisation for the above mentioned veterinary medicinal product which falls within the scope of Part B of the annex to Council Regulation (EEC) No 2309/93.

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London, 14 October 1998

On behalf of the CVMP
Prof. R. Kroker, Chairman

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ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

Confidential
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1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 50% premix for medicated feed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Econor 50% premix contains valnemulin in the form of valnemulin hydrochloride.

2.1 Active substance

Valnemulin hydrochloride	532.5 mg/g
equivalent to	500 mg/g valnemulin base

2.2 Excipients knowledge of which is essential for the proper administration of the veterinary medicinal product

Hypromellose and talc

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PHARMACOLOGICAL PROPERTIES

Valnemulin is an antibiotic belonging to the pleuromutilin group, which acts by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
Valnemulin has activity against a range of bacteria including those responsible for enteric and respiratory disease in pigs.

Valnemulin shows high activity against *Mycoplasma spp.* and spirochaetes such as *Serpulina hyodysenteriae.*

Species	MIC (Range) (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Mycoplasma hyopneumoniae *Serpulina hyodysenteriae*	0.0009 - 0.125 0.025 - 4.0	0.0025 0.2	0.01 1.0

Valnemulin has little activity against *Enterobacteriaceae*, such as *Salmonella spp.* and *Escherichia coli*.

In pigs, after a single oral dose of radiolabelled material >90% absorption was demonstrated. Maximum plasma concentrations (C_{max}) of radio-labelled or 'cold' material were obtained 1-4 hours after dosing (T_{max}) with a plasma half-life (t½), estimated from non-radioactive data, between 1 and 4½ hours. A linear relationship between concentration and dose administered was established.

After repeat dosing, slight accumulation occurred, but a steady state was achieved within 5 days.

Because of a marked 'first pass' effect, plasma concentrations are affected by the method of administration, but valnemulin is highly concentrated in tissues, particularly the lungs and liver, relative to plasma. Five days after the last of 15 doses of radiolabelled valnemulin administered to pigs, the concentration in liver was >6 times that in plasma. Two hours after withdrawal of

Premix given in feed twice daily for 4 weeks at a dose of 15 mg/kg/day, liver concentration was 1.58 μg/g and lung concentration 0.23 μg/g whereas concentrations in plasma were below the limit of detection.

In pigs valnemulin is extensively metabolised and excretion of parent molecule and metabolites occurs mainly via bile. 73% - 95% of the daily dose of total radioactivity was recovered from the faeces. The plasma half-life was 1.3 – 2.7 hours, and the majority of the total radio-activity administered was excreted within 3 days of the last administration.

5. CLINICAL PARTICULARS

5.1 Target species

Pigs

5.2 Indications for use, specifying the target species

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.

5.3 Contraindications

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

5.4 Undesirable effects (frequency and seriousness)

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well-accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

5.5 Special precaution for use

None

5.6 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.

5.7 Interaction with other veterinary medicinal products and other forms of interaction

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.

5.8 Posology and method of administration

For oral use. The dosage is 10 – 12 mg/kg bodyweight per day. This is normally achieved, for example, in grower pigs, by incorporating Econor 50% at a level of 400 g/tonne feed to provide 200 mg active substance per kg feed depending on pigs' feed intake.

Mg valnemulin base/kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)
The medicated feed should be fed as the sole ration daily for up to 3 weeks. In older pigs, or in pigs with reduced appetite or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Mixing Instructions:

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

To achieve good mixture and homogeneity of incorporation, the use of a pre-mixture is highly recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 50% to 20 parts feed ingredient.

5.9 Overdose

Toxic signs have not been seen in pigs given 5 times the recommended dose.

5.10 Special warnings for each target species

None

5.11 Withdrawal period

4 days

5.12 Special precautions to be taken by the person administering the veterinary medicinal product to animals.

When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label. People with known hypersensitivity to valnemulin should administer the product with caution.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

None known

6.2 Shelf life, when necessary after reconstitution of the veterinary medicinal product or when the container is opened for the first time

3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

6.3. Special precautions for storage

Store below 25°C.
In case of aluminium-lined bags, store product in the original container.
In case of polyethylene bags, store the product in the original container within the outer carton and protected from light and moisture.
Part-used containers should be tightly closed following dispensing.

6.4 Nature and contents of container

1 kg and 25 kg low density polyethylene bags packed in cardboard carton or 1 kg and 25 kg aluminium-lined plastic bags.

6.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from such medicinal products, if appropriate

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Animal Health Austria GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

[leave blank]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[leave blank]

10. DATE OF REVISION OF THE TEXT

[leave blank]

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 10% premix for medicated feed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Econor 10% premix contains valnemulin in the form of valnemulin hydrochloride.

2.1 Active substance

Valnemulin hydrochloride 106.5 mg/g
equivalent to 100 mg/g valnemulin base

2.2 Excipients knowledge of which is essential for the proper administration of the veterinary medicinal product

Hypromellose and talc
Colloidal anhydrous silica
Isopropyl myristate
Lactose

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PHARMACOLOGICAL PROPERTIES

Valnemulin is an antibiotic belonging to the pleuromutilin group, which act by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
Valnemulin has activity against a range of bacteria including those responsible for enteric and respiratory disease in pigs.

Valnemulin shows high activity against *Mycoplasma spp.* and spirochaetes such as *Serpulina hyodysenteriae.*

Species	MIC (Range) (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Mycoplasma hyopneumoniae	0.0009 - 0.125	0.0025	0.01
Serpulina hyodysenteriae	0.025 - 4.0	0.2	1.0

Valnemulin has little activity against *Enterobacteriaceae*, such as *Salmonella spp.* and *Escherichia coli*.

In pigs, after a single oral dose of radiolabelled material >90% absorption was demonstrated. Maximum plasma concentrations (C_{max}) of radiolabelled or 'cold' material were obtained 1-4 hours after dosing (T_{max}) with a plasma half-life (t½), estimated from non-radioactive data, between 1 and 4½ hours. A linear relationship between concentration and dose administered was established.

After repeat dosing, slight accumulation occurred, but a steady state was achieved within 5 days.

Because of a marked 'first pass' effect, plasma concentrations are affected by the method of administration, but valnemulin is highly concentrated in tissues, particularly the lungs and liver, relative to plasma. Five days after the last of 15 doses of radiolabelled valnemulin administered to pigs, the concentration in liver was >6 times that in plasma. Two hours after withdrawal of Premix given in feed twice daily for 4 weeks at a dose of 15 mg/kg/day, liver concentration was 1.58 μg/g and lung concentration 0.23 μg/g whereas concentrations in plasma were below the limit of detection.

In pigs valnemulin is extensively metabolised and excretion of parent molecule and metabolites occurs mainly via bile. 73% - 95% of the daily dose of total radioactivity was recovered from the faeces. The plasma half-life was 1.3 – 2.7 hours, and the majority of the total radio-activity administered was excreted within 3 days of the last administration

5. CLINICAL PARTICULARS

5.1 Target species

Pigs

5.2 Indications for use, specifying the target species

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

5.3 Contraindications

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

5.4 Undesirable effects (frequency and seriousness)

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

5.5 Special precaution for use

None

5.6 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.

5.7 Interaction with other veterinary medicinal products and other forms of interaction

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.

5.8 Posology and method of administration

For oral use.
Treatment of swine dysentery: The dosage is 3 – 4 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 10% at a level of 750 g/tonne feed to provide 75 mg active substance per kg feed. 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 medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. It is important to institute medication as early as possible in an outbreak of swine dysentery. In pigs with reduced appetite or on restricted feed, inclusion levels may need to be increased to achieve target dosage. If there is no response to treatment within 5 days, the diagnosis should be re-established

Prevention of swine dysentery:
The dosage is 1 – 1.5 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 10% premix with the final feed at a level of 250 g/tonne feed to provide 25 mg active substance per kg feed. The medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. Long term preventative use of valnemulin should be avoided by improving management practice and thorough cleansing and disinfection. Consideration should be given to the eradication of infection from the farm.

Treatment and prevention of swine enzootic pneumonia: The dosage is 10 – 12 mg/kg bodyweight per day. This is normally achieved, for example, in grower pigs, by incorporating Econor 10% at a level of 2 kg/tonne feed to provide 200 mg active substance per kg feed depending on pigs' feed intake.

Mg valnemulin base / kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)

The medicated feed should be fed as the sole ration daily. In older pigs, or in pigs with reduced appetite or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Mixing Instructions:

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

To achieve good mixture and homogeneity of incorporation, the use of a pre-mixture is recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 10% Premix to 10 parts feed ingredient.

5.9 Overdose

Toxic signs have not been seen in pigs given 5 times the recommended dose.

5.10 Special warnings for each target species

None

5.11 Withdrawal period

4 days

5.12 Special precautions to be taken by the person administering the veterinary medicinal product to animals.

When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label. People with known hypersensitivity to valnemulin should administer the product with caution.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

None known

6.2 Shelf life, when necessary after reconstitution of the veterinary medicinal product or when the container is opened for the first time

3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

6.3. Special precautions for storage

Store below 25°C.
In case of aluminium-lined bags, store product in the original container.
In case of polyethylene bags, store the product in the original container within the outer carton and protected from light and moisture.
Part-used containers should be tightly closed following dispensing.

6.4 Nature and contents of container

1 kg and 25 kg low density polyethylene bags packed in cardboard carton or 1 kg and 25 kg aluminium-lined plastic bags.

6.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from such medicinal products, if appropriate

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Animal Health Austria GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

[leave blank]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[leave blank]

10. DATE OF REVISION OF THE TEXT

[leave blank]

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 1% premix for medicated feed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Econor 1% Premix contains valnemulin in the form of valnemulin hydrochloride.

2.1 Active substance

Valnemulin hydrochloride 10.65 mg/g
equivalent to 10 mg/g valnemulin base

2.2 Excipients knowledge of which is essential for the proper administration of the veterinary medicinal product

Hypromellose and talc
Colloidal anhydrosus silicum
Isopropyl myristate
Lactose

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PHARMACOLOGICAL PROPERTIES

Valnemulin is an antibiotic belonging to the pleuromutilin group, which act by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
Valnemulin has activity against a range of bacteria including those responsible for enteric and respiratory disease in pigs.

Valnemulin shows high activity against *Mycoplasma spp.* and spirochaetes such as *Serpulina hyodysenteriae.*

Species	MIC (Range) (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Mycoplasma hyopneumoniae	0.0009 - 0.125	0.0025	0.01
Serpulina hyodysenteriae	0.025 - 4.0	0.2	1.0

Valnemulin has little activity against *Enterobacteriaceae*, such as *Salmonella spp.* and *Escherichia coli*.

In pigs, after a single oral dose of radiolabelled material >90% absorption was demonstrated. Maximum plasma concentrations (C_{max}) of radio-labelled or 'cold' material were obtained 1-4 hours after dosing (T_{max}) with a plasma half-life ($t_{½}$), estimated from non-radioactive data, between 1 and 4½ hours. A linear relationship between concentration and dose administered was established.

After repeat dosing, slight accumulation occurred, but a steady state was achieved within 5 days.

Because of a marked 'first pass' effect, plasma concentrations are affected by the method of administration, but valnemulin is highly concentrated in tissues, particularly the lungs and liver, relative to plasma. Five days after the last of 15 doses of radio-labelled valnemulin administered to pigs, the concentration in liver was >6 times that in plasma. Two hours after withdrawal of Premix given in feed twice daily for 4 weeks at a dose of 15 mg/kg/day, liver concentration was 1.58 μg/g and lung concentration 0.23 μg/g whereas concentrations in plasma were below the limit of detection.

In pigs valnemulin is extensively metabolised and excretion of parent molecule and metabolites occurs mainly via bile. 73% - 95% of the daily dose of total radioactivity was recovered from the faeces. The plasma half-life was 1.3 – 2.7 hours, and the majority of the total radio-activity administered was excreted within 3 days of the last administration.

5. CLINICAL PARTICULARS

5.1 Target species

Pigs

5.2 Indications for use, specifying the target species

For the treatment and prevention of swine dysentery.

5.3 Contraindications

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

5.4 Undesirable effects (frequency and seriousness)

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

5.5 Special precaution for use

None

5.6 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.

5.7 Interaction with other veterinary medicinal products and other forms of interaction

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.

5.8 Posology and method of administration

For oral use.
Treatment of swine dysentery:
The dosage is 3 – 4 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 1% premix at a level of 7.5 kg/tonne feed to provide 75mg active substance per kg feed. 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 medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. It is important to institute medication as early as possible in an outbreak of swine dysentery. In pigs with reduced appetite or on restricted feed, inclusion levels may need to be increased to achieve target dosage. If there is no response to treatment within 5 days, the diagnosis should be re-established.

Prevention of swine dysentery:
The dosage is 1 – 1.5 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 1% premix with the final feed at a level of 2.5 kg/tonne feed to provide 25 mg active substance per kg feed. The medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. Long term preventative use of valnemulin should be avoided by improving management practice and thorough cleansing and disinfection. Consideration should be given to the eradication of infection from the farm.

Mg valnemulin base/kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)

Mixing Instructions:

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.

To achieve good mixture and homogeneity of incorporation, especially when product is incorporated at a rate less then 5kg/tonne feed, the use of a pre-mixture is recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 1% Premix to 10 parts feed ingredient.

5.9 Overdose

Toxic signs have not been seen in pigs given 5 times the recommended dose.

5.10 Special warnings for each target species

None

5.11 Withdrawal period

1 day

5.12 Special precautions to be taken by the person administering the veterinary medicinal product to animals.

When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label. People with known hypersensitivity to valnemulin should administer the product with caution.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

None known

6.2 Shelf life, when necessary after reconstitution of the veterinary medicinal product or when the container is opened for the first time

3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

6.3. Special precautions for storage

Store below 25°C.
In case of aluminium-lined bags, store product in the original container.
In case of polyethylene bags, store the product in the original container within the outer carton and protected from light and moisture.
Part-used containers should be tightly closed following dispensing.

6.4 Nature and contents of container

1 kg, 2.5 kg and 25 kg low density polyethylene bags packed in cardboard carton or 1 kg, 2.5 kg and 25 kg aluminium-lined plastic bags.

6.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from such medicinal products, if appropriate

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Animal Health Austria GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

[leave blank]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[leave blank]

10. DATE OF REVISION OF THE TEXT

[leave blank]

ANNEX II
THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE AND CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for batch release

Biochemie Gesellschaft MBH
Schaftenau Plant
A-6330 Schaftenau
Austria

Manufacturing Authorisation issued in October 1995 by the Austrian Federal Ministry of Health, Sport and Consumer Protection.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. PROHIBITION OF SALE, SUPPLY AND/OR USE

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

D. STATEMENT OF THE MRLs WHICH MAY BE ACCEPTED IN ACCORDANCE WITH COUNCIL REGULATION (EEC) No 2377/90

Annex I, II or III of Council Regulation (EEC) No 2377/90

Pharmacologically active substance	Animal Species	Other provisions
Valnemulin hydrochloride[1]	Pigs	
Hypromellose [2]	All food-producing species	
Purified Talc [3]	All food-producing species	

[1] Annex I recommendation adopted at the CVMP meeting in May 1998
[2] OJ No. L 272 of 25.10.96
[3] OJ No. L 272 of 25.10.96

ANNEX III
LABELLING AND PACKAGE INSERT

(Note - Labelling is presented for only one pack size of each strength of product as a relevant example.)

In accordance with Article 48 of Council Directive 81/851/EEC the inclusion of a Package Insert in the packaging of the veterinary medicinal product shall not be obligatory, as all the information required is conveyed on the container or the outer package of the veterinary medicinal product.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE OR, WHERE THERE IS NO OUTER PACKAGE, ON THE IMMEDIATE PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 50% premix for medicated feed

2. STATEMENT OF THE ACTIVE SUBSTANCE

Econor 50% premix contains valnemulin in the form of valnemulin hydrochloride.

Valnemulin hydrochloride	532.5 mg/g
equivalent to	500 mg/g valnemulin base
Hypromellose and talc	

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PACKAGE SIZE

1 kg

5. TARGET SPECIES

Pigs

6. INDICATIONS

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.

7. DOSAGE FOR EACH SPECIES

The dosage is 10 – 12 mg/kg bodyweight per day.

8. METHOD AND ROUTE OF ADMINISTRATION

For oral use.

9. ADVICE ON CORRECT ADMINISTRATION

For oral use. The dosage is 10 – 12 mg/kg bodyweight per day. This is normally achieved, for example, in grower pigs, by incorporating Econor 50% at a level of 400 g/tonne feed to provide 200 mg active substance per kg feed depending on pigs' feed intake.

Mg valnemulin base/kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)

The medicated feed should be fed as the sole ration daily for up to 3 weeks. In older pigs, or in pigs with reduced appetite or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Mixing Instructions:

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

To achieve good mixture and homogeneity of incorporation, the use of a pre-mixture is highly recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 50% to 20 parts feed ingredient.

10. CONTRA-INDICATIONS

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

11. UNDESIRABLE EFFECTS

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well-accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

12. WITHDRAWAL PERIOD

4 days

13. SPECIAL STORAGE CONDITIONS

Store below 25°C.
In case of aluminium-lined bags, store product in the original container.
In case of polyethylene bags, store the product in the original container within the outer carton and protected from light and moisture.
Part-used containers should be tightly closed following dispensing.

Shelf life:
3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

14. SPECIAL WARNINGS

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.

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.

When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label. People with known hypersensitivity to valnemulin should administer the product with caution.

15. EXPIRY DATE

{month/year}

16. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

17. THE WORDS "KEEP OUT OF THE REACH OF CHILDREN"

Keep out of the reach of children.

18. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

19. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Novartis Animal Health Austria GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

20. DATE ON WHICH THE PACKAGE INSERT WAS LAST REVISED

[leave blank]

21. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

[leave blank]

22. MANUFACTURER'S BATCH NUMBER

[leave blank]

23. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.
Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

24. OTHER INFORMATION

Valnemulin is an antibiotic belonging to the pleuromutilin group, which acts by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

Belgique/België
NOVARTIS AGRO Benelux B.V.
Animal Health Sector
Stepvelden 10
NL - 4704Roosendaal
Tel.: 0031- (0) 165.547804(5)

Danmark
NOVARTIS Agri A/S
Sector Animal Health
Lyngbyvej 172
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Tel.: 39 16 84 00

Deutschland
Novartis Tiergesundheit GmbH
Industriestrasse 30-34
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Novartis (Hellas) S.A.C.I
Anthoussas Ave.
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España
NOVARTIS Sanidad Animal, S.L.
Carrer de la Marina, 206
E - 08013 Barcelona
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F - 92845 Rueil Malmaison
Tel.: 01 55 47 87 15

Ireland
Novartis Agribusiness Ireland Limited
Industrial Park
IRL - Waterford
Tel.: 051 377201

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Novartis Animal Health S.p.A.
Strada Statale 233 km 20,5
I - 21040 Origgio (VA)
Tel.: 02-96542886

Luxembourg
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Animal Health Sector
Stepvelden 10
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Tel.: 0031- (0) 165.547804(5)

Nederland
NOVARTIS AGRO Benelux B.V.
Animal Health Sector
Stepvelden 10
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Österreich
NOVARTIS Animal Health GmbH
Biochemiestrasse 10
A-6250 Kundl
Tel.: 0043-5338-200425

Portugal
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Rua Castilho 5, S-19
P - 1250 Lisboa
Tel.: (351-1) 355 20 80

Suomi/Finland
NOVARTIS Finland OY
Animal Health Sector
Metsänneidonkuja 10
FIN - 02130 Espoo
Puh. (09) 6133 2211

Sverige
NOVARTIS Sverige AB
Veterinärmedicin
Kungsporten 4A
S - 427 50 Billdal
Tel.: 031-93 95 47

United Kingdom
Novartis Animal Health (UK) Limited
Whittlesford
GB - Cambridge CB2 4QT
Tel.: 01223 833634

PARTICULARS TO APPEAR ON THE OUTER PACKAGE OR, WHERE THERE IS NO OUTER PACKAGE, ON THE IMMEDIATE PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 10% premix for medicated feed

2. STATEMENT OF THE ACTIVE SUBSTANCE

Econor 10% premix contains valnemulin in the form of valnemulin hydrochloride.
Valnemulin hydrochloride 106.5 mg/g
equivalent to 100 mg/g valnemulin base

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PACKAGE SIZE

1 kg

5. TARGET SPECIES

Pigs

6. INDICATIONS

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

7. DOSAGE FOR EACH SPECIES

Treatment of swine dysentery: The dosage is 3 – 4 mg/kg bodyweight per day
Prevention of swine dysentery: The dosage is 1 – 1.5 mg/kg bodyweight per day
Treatment and prevention of swine enzootic pneumonia: The dosage is 10 – 12 mg/kg bodyweight per day

8. METHOD AND ROUTE OF ADMINISTRATION

For oral use

9. ADVICE ON CORRECT ADMINISTRATION

Treatment of swine dysentery: The dosage is 3 – 4 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 10% at a level of 750 g/tonne feed to provide 75 mg active substance per kg feed. 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 medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. It is important to institute medication as early as possible in an outbreak of swine dysentery. In pigs with reduced appetite or on restricted feed, inclusion levels may need to be increased to achieve target dosage. If there is no response to treatment within 5 days, the diagnosis should be re-established

Prevention of swine dysentery:
The dosage is 1 – 1.5 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 10% premix with the final feed at a level of 250 g/tonne feed to provide 25 mg active substance per kg feed. The medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. Long term preventative use of valnemulin should be avoided by improving management practice and thorough cleansing and disinfection. Consideration should be given to the eradication of infection from the farm.

Treatment and prevention of swine enzootic pneumonia: The dosage is 10 – 12 mg/kg bodyweight per day. This is normally achieved, for example, in grower pigs, by incorporating Econor 10% at a level of 2 kg/tonne feed to provide 200 mg active substance per kg feed depending on pigs' feed intake.

Mg valnemulin base / kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)

The medicated feed should be fed as the sole ration daily. In older pigs, or in pigs with reduced appetite or on restricted feed intake, inclusion levels may need to be increased to achieve target dosage.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Mixing Instructions:

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

To achieve good mixture and homogeneity of incorporation, the use of a pre-mixture is recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 10% Premix to 10 parts feed ingredient.

10. CONTRA-INDICATIONS

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

11. UNDESIRABLE EFFECTS

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

12. WITHDRAWAL PERIOD

4 days

13. SPECIAL STORAGE CONDITIONS

Store below 25°C.
In case of aluminium-lined bags, store product in the original container.
In case of polyethylene bags, store the product in the original container within the outer carton and protected from light and moisture.
Part-used containers should be tightly closed following dispensing.

Shelf life:

3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

14. SPECIAL WARNINGS

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.

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.

When mixing the product and handling the final feed containing the product, direct contact with the skin and mucous membranes should be avoided. In case of accidental ingestion, seek medical advice immediately and show the product label. People with known hypersensitivity to valnemulin should administer the product with caution.

15. EXPIRY DATE

{month/year}

16. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

17. THE WORDS "KEEP OUT OF THE REACH OF CHILDREN"

Keep out of the reach of children.

18. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCT OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

19. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Novartis Animal Health Austria GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

20. DATE ON WHICH THE PACKAGE INSERT WAS LAST REVISED

[leave blank]

21. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

[leave blank]

22. MANUFACTURER'S BATCH NUMBER

[leave blank]

23. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.
Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds**.**

24. OTHER INFORMATION

Valnemulin is an antibiotic belonging to the pleuromutilin group, which act by the inhibition of the initiation of protein synthesis at the level of the bacterial ribosome.
For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Whittlesford
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Tel.: 01223 833634

PARTICULARS TO APPEAR ON THE OUTER PACKAGE OR, WHERE THERE IS NO OUTER PACKAGE, ON THE IMMEDIATE PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Econor 1% premix for medicated feed

2. STATEMENT OF THE ACTIVE SUBSTANCE

Econor 1% premix contains valnemulin in the form of valnemulin hydrochloride.

Valnemulin hydrochloride	10.65 mg/g
equivalent to	10 mg/g valnemulin base

3. PHARMACEUTICAL FORM

Premix for medicated feed

4. PACKAGE SIZE

1 kg

5. TARGET SPECIES

Pigs

6. INDICATIONS

For the treatment and prevention of swine dysentery.

7. DOSAGE FOR EACH SPECIES

Treatment of swine dysentery: The dosage is 3 – 4 mg/kg bodyweight per day.
Prevention of swine dysentery: The dosage is 1 – 1.5 mg/kg bodyweight per day.

8. METHOD AND ROUTE OF ADMINISTRATION

For oral use

9. ADVICE ON CORRECT ADMINISTRATION

Treatment of swine dysentery: The dosage is 3 – 4 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 1% premix at a level of 7.5 kg/tonne feed to provide 75 mg active substance per kg feed. 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 medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. It is important to institute medication as early as possible in an outbreak of swine dysentery. In pigs with reduced appetite or on restricted feed, inclusion levels may need to be increased to achieve target dosage. If there is no response to treatment within 5 days, the diagnosis should be re-established.

Prevention of swine dysentery:
The dosage is 1 – 1.5 mg/kg bodyweight per day. This is normally achieved by incorporating Econor 1% premix with the final feed at a level of 2.5 kg/tonne feed to provide 25 mg active substance per kg feed. The medicated feed should be fed as the sole ration daily for a minimum of 7 days and up to 4 weeks or until signs of disease disappear. Long term preventative use of valnemulin should be avoided by improving management practice and thorough cleansing and disinfection. Consideration should be given to the eradication of infection from the farm.

Mg valnemulin base/kg feed = Dosage required (mg/kg) X 1,000 X bodyweight (kg) / Daily feed intake (grams)

Mixing Instructions:

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To achieve good mixture and homogeneity of incorporation, especially when product is incorporated at a rate less then 5 kg/tonne feed, the use of a pre-mixture is recommended. The required quantity of product is thoroughly mixed with a feed ingredient of similar physical nature (e.g. wheat middlings) in the proportion: 1 part Econor 1% Premix to 10 parts feed ingredient.

10. CONTRA-INDICATIONS

Do not administer the product to pigs receiving ionophore antibiotics.
Valnemulin should not be administered to rabbits because of its toxicity in this species.

11. UNDESIRABLE EFFECTS

On rare occasions perianal erythema or mild oedema of the skin may occur in pigs following the use of valnemulin. If such signs are seen, immediately withdraw all remaining medicated feed, remove to clean dry surroundings and apply appropriate supportive symptomatic therapy in affected pigs.
Valnemulin is well accepted in feed, but administered at concentrations above 200 ppm may result in transient reduction in food consumption associated with unpalatability during the first few days of feeding.

12. WITHDRAWAL PERIOD

1 day

13. SPECIAL STORAGE CONDITIONS

Store below 25°C.
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Part-used containers should be tightly closed following dispensing.

Shelf life:

3 years
3 months, when incorporated into meal feed and protected from light and moisture.
3 weeks, when incorporated into pelleted feed and protected from light and moisture.

14. SPECIAL WARNINGS

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15. EXPIRY DATE

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24. OTHER INFORMATION

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For any information about this veterinary medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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