EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report
Econor oral powder (EMEA/V/C/042/X/033)

International non-proprietary name: Valnemulin

Scope: new pharmaceutical form (oral powder)

Assessment Report as adopted by the CVMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Product profile

Invented name:	Econor
Active Substances:	Valnemulin
Target Species:	Pigs
Pharmaceutical Form:	Oral powder
Strength:	10 %
Therapeutic Indication:	Treatment of: • Swine Dysentery • Clinical signs of Porcine Proliferative Enteropathy (ileitis). • Swine Enzootic Pneumonia.
ATCvet code	QJ01XQ02
Pharmaco-Therapeutic Group	Antibacterials for systemic use, Pleuromutilins
Applicant	Novartis Animal Health Biochemiestrasse 10 A-6250 Kundl Austria

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1. Background information on the procedure

1.1. Steps taken for the assessment of the product

The Committee for Medicinal Products for Veterinary Use confirmed Ruth Kearsley from UK as Rapporteur and Jean-Pierre Binder from Austria as Co-Rapporteur for the assessment of the application for Econor during its meeting of 9-11 December 208.

The company Novartis Animal Health GmbH Austria submitted an application to the European Medicines Agency (the Agency) on 5 May 2009 for an extension of the Community marketing authorisation for Econor, in accordance with Annex I of Regulation 1234/2008. The application was validated on 19 May 2009.

1.2. Steps taken for the assessment of the product

- The rapporteur and co-rapporteur's assessment reports were circulated to all CVMP Members on 28 July 2009 and 12 August 2009, respectively.
- The consolidated list of questions as agreed by the CVMP during its meeting held in September 2009 was sent to the applicant and the clock stopped.
- The applicant circulated the responses to the CVMP list of questions on 15 April 2010 and the 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 all CVMP Members on 21 May 2010.
- During their plenary meeting held in June 2010, the CVMP decided that an oral explanation was required and agreed a List of outstanding issues.
- During their plenary meeting in September 2010, the CVMP considered the responses given by the applicant in writing and at an Oral Explanation.
- 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 12 October 2010, a positive opinion for the extension of the marketing authorisation for Econor.
- On 6 January 2011 the European Commission issued a Commission Decision for this extension.

1.3. Administrative particulars

1.3.1. Conditions regarding the pharmacovigilance system

The detailed description of the pharmacovigilance system in place is considered satisfactory.

1.3.2. GMP inspections of the manufacturing sites

The GMP status of the dosage form manufacturing, assembly and release sites is satisfactory.

2. Quality assessment

Econor oral powder is identical in terms of its formulation, manufacture and control to the currently authorised product Econor 10% premix for medicated feeding stuff ("premix") for pigs and can, therefore, be concluded to be essentially of satisfactory quality and does not present a TSE risk.

The pack is identical in size and material of construction to one of those used for Econor 10% premix, i.e. 1 kg. The applicant has, based on different feeding scenarios, described and justified the pack size, which has been shown appropriate for use in individual pigs on farms where only a small number of pigs are to receive the medicine. Each bag is supplied with two measuring scoops for which acceptable dose accuracy and precision have been shown. The measuring spoons are fixed to the primary pack ensuring that they will be available to the end user.

The release and shelf-life specifications are based upon those for Econor 10% premix, supplemented with tests for microbial purity and bulk density. The absence of a test for particle size has been justified. Acceptably, no data were supplied concerning the analytical methods as these are unchanged from those used for Econor 10% premix. Batch analysis data were presented for three batches manufactured in 2008. The data show consistency of manufacture.

Since the pack is the same as one of those used for Econor 10% premix, the same shelf life is considered appropriate. Acceptably, no stability data on the product stored in unopened packs were supplied.

The stability of valnemulin in various types of dry pig feed was evaluated during the CVMP assessment of Econor premixes. These data are considered to apply equally to Econor oral powder. Data were also presented on the stability of valnemulin from Econor 10 % in wet (liquid) feed at a concentration of 0.2 mg valnemulin/kg of wet feed. The feed was a commercial feed available in The Netherlands and was adjusted to 3 pH values: 3.5, 4.5 and 5.5. After 24 hours storage the valnemulin content of the wet feed remained at greater than 89 % of the target concentration when analysed using a microbiological method which was considered adequate for determination of valnemulin in feed. The data show that the use of Econor 10% oral powder in liquid feed based upon water and milk co-products is acceptable.

An in-use stability study has been carried out. Results support an in-use shelf life of six months provided the product is stored in the original container and tightly closed following dispensing. The warning "Store the product in the original container" was therefore added to the SPC and product literature.

3. Safety assessment

This extension application was submitted to add a new pharmaceutical form for Econor, i.e. Econor 10% oral powder for pigs. Accordingly, there is no change to the currently authorised claims in terms of clinical indications or dosages. Furthermore, the 10% oral powder formulation is identical to the already authorised premix presentation of the same strength.

As the proposed product formulation and dosage regimen (route/dose/frequency/duration) for this extension are identical to those of the already authorised 10% premix, documentation in support of safety has previously been submitted as either part of the original marketing authorisation application (EMEA/V/C/042) or the maximum residue limit application (EU/96/022/SDZ). Data were therefore not re-presented but instead cross-reference to the appropriate application was made.

Pharmacodynamics

The pharmacodynamic data submitted with the original application are relevant to this extension application. As this product is identical to that already authorised and the same dosage and route of administration are used for this new pharmaceutical form, no new data were required.

Pharmacokinetics

The pharmacokinetic data submitted with the original application are relevant to this extension application. As this product is identical to that already authorised and the same dosage and route of administration are used for this new pharmaceutical form, no new data were required.

Toxicology

The toxicological data submitted with the original application are relevant to this extension application. As this product is identical to that already authorised and the same dosage and route of administration are used for this new pharmaceutical form, no new data were required. However, since the original application for marketing authorisation the applicant conducted one additional mutagenicity study which is summarised below.

Mutagenicity/genotoxicity

Valnemulin was evaluated for mutagenic activity at the thymidine kinase locus of L5178Y mouse lymphoma cells by means of a fluctuation protocol. Concentrations ranging from 0.2 to 90 µg/ml were used in the range of experiments both with and without metabolic activation. Valnemulin was found to be cytotoxic within the concentration range tested but clearly demonstrated the absence of any mutagenic potential at the thymidine kinase locus of L5178Y mouse lymphoma cells under all of the test conditions.

Studies of other effects

Although, as for other aspects of safety, no new information was required, the applicant submitted the reports of four new studies which had been conducted since the original application for marketing authorisation. These studies included acute dermal toxicity in rats, acute dermal irritation in rabbits, contact hypersensitivity in albino guinea pigs and a local lymph node assay. All studies were conducted in accordance with GLP and followed the relevant OECD guidelines.

The results showed that valnemulin was of very low acute dermal toxicity in rats and was non-irritating to the skin of rabbits. Both of the hypersensitivity tests (maximization test and local lymph node assay) also showed that valnemulin was not a sensitizer in these test systems.

User safety

The product is an oral powder for in-feed use for pigs. It is intended to be used in individual animals or small numbers of animals. The animals are given the required dose by inclusion of the required amount in the daily ration.

Unlike the already authorised premix, this product is added to the feed by the person administering the feed to pigs. On the other hand, it is intended to be administered to smaller numbers of animals than the premix. Thus, the exposure assessment is slightly different from that for the premix. Nevertheless, the potential exposure during handling and administration of the oral powder will be limited, and

additional studies confirmed that valnemulin has low acute dermal toxicity and is neither an irritant nor a sensitizer. It was therefore concluded that the same user warnings as the ones currently agreed for the premix range of products were appropriate for the oral powder too.

Environmental risk assessment

Econor 10% oral powder was developed as a line extension to Econor 0.5%, 1%, 10% and 50% premix for medicated feedingstuff. The product is intended for use in individual pigs on farms where only a small number of animals are to be treated. It will be given to individual or small numbers of animals only, which will be dosed individually. The target species, indications, dose, duration of treatment and route of administration are the same as for the already authorised premix products.

Consequently, exposure of the environment from the use of this product will not increase or change when compared with the exposure resulting from use of the premix products. The environmental risk assessment for the premix products was considered to be acceptable when it was evaluated during the assessment of these products.

As there is no increase or change in exposure following the use of Econor 10% oral powder it can be concluded that the use of the product is not expected to pose a risk for the environment when used in accordance with the SPC.

RESIDUES DOCUMENTATION

Identification of the product concerned

This application is for an extension to the authorised Econor premix for medicated feed for pigs to support an additional pharmaceutical form for the product, namely Econor 10% oral powder for Pigs. Accordingly, there is no change to the currently authorised claims in terms of clinical indications or dosages. Furthermore, the 10% oral powder formulation is identical to the already authorised premix presentation of the same strength.

As the proposed product formulation and dosage regime (route/dose/frequency/duration) for this extension are identical to those of the already authorised Econor 10% premix, documentation in support of consumer safety have previously been submitted as either part of the original Marketing Authorisation application or the MRL application. Data in this section were therefore not re-presented but instead cross-reference to the appropriate application was made.

Residue studies

No further information is necessary as this product is identical to the already authorised 10% premix, and the same dosage and route of administration are used for this new pharmaceutical form.

The same withdrawal period of 1 day is therefore acceptable.

Analytical methods

The analytical method has already been validated and accepted.

Overall conclusions on the safety documentation

User Risk Assessment:

The use of this new pharmaceutical form (oral powder) will not increase exposure to the user when compared to the use of the premix range of products. Therefore, the currently agreed user warnings for the premix are generally considered to be appropriate for the oral powder.

Environmental Risk Assessment:

The use of Econor 10% oral powder is not expected to pose a risk for the environment when used in accordance with the SPC.

Residues Assessment:

The use of this new pharmaceutical form (oral powder) will not increase the residue levels as this product is identical to the already authorised premix and the same dosage, route of administration and withdrawal period are used for this new pharmaceutical form as for the premix.

Part 4 – Efficacy

Econor 10% oral powder is the same formulation as the 10% premix, but is intended for the treatment of individual pigs, by administration to the animal's daily feed ration. The indications and dose regimen are the same as those of the premix, except that no prevention claim is sought. The applicant therefore made cross-reference to data submitted previously. Some new data were also submitted.

Pharmacodynamics

Valnemulin is a pleuromutilin antibiotic which acts by the inhibition of protein synthesis at the level of the bacterial ribosome. Cross reference was made to the Clinical and Safety Expert Statement submitted for the Econor renewal, but the applicant also submitted several recent literature references and their own new study which investigated the susceptibility of *Brachyspira hyodysenteriae (B. hyo), B. pilosicoli (B. pilo)* spp and *Mycoplasma hyopneumoniae (M. hyo)* to valnemulin (Pridmore 2008).

Based on these studies, the wild-type MICs and MIC_{90}s for the target pathogens are as follows:

Species	MIC of wild-type population (µg/ml)	MIC_{90} (µg/ml)
Brachyspira hyodysenteriae	≤0.125	2.0
Brachyspira pilosicoli	≤0.125	0.5
Mycoplasma hyopneumoniae	≤0.008	0.004

The intracellular MIC for all strains of *Lawsonia intracellularis (Li)* was ≤ 0.125 µg/ml.

The applicant also provided calculations for PK-PD integrations, however, these are considered to be of limited value for dose finding for *M. hyopneumoniae* and *L. intracellularis* because of the organisms' intracellular location. The PK-PD indices and their values were not validated for the *Brachyspira*-valnemulin combinations, and these integrations are therefore also considered to be speculative in predicting the dosage schedule.

Development of resistance

Literature references advise that resistance to pleuromutilins can develop in *B. hyopneumoniae* by a chromosomal mutation, which results in alteration of the drug-binding site on the bacterial ribosome. The MIC data provided indicate the emergence of valnemulin-resistant strains of *Brachyspira spp*. since Econor was first authorised. It was agreed that lack of standardisation of MIC testing for *Brachyspira* caused problems with structured surveillance. Literature references provided evidence of cross-resistance between valnemulin and tiamulin in *Brachyspira* spp.

There is no evidence to date of resistance to valnemulin in *M. hyopneumoniae* and *L. intracellularis*.

Target Animal Tolerance

The applicant cross-referred to data submitted in previous applications. In a preliminary safety study valnemulin at an inclusion rate of 1500 mg/kg feed (ca. 6 x max RTD) caused an initial drop in feed intake which was attributed to lack of palatability. In another study, a dose of 15 mg valnemulin/kg bw (x 4 weeks) was considered to be the NOAEL in pigs. At a dose rate from 45 mg/kg bw, early signs of toxicity appeared (effects on faecal appearance, bodyweight gain and liver enzymes). These effects were more marked at 75 mg/kg, but there were no serious toxic effects or mortalities at this dose. As the dose rate of the oral powder is the same as that for the premix, and bioavailability can be assumed to be the same, there should be no change in the assessment of target animal safety.

Dose justification and Clinical Documentation

The applicant has cross-referred to the data submitted for the data submitted in support of the initial (Swine dysentery and Enzootic pneumonia) and post-authorisation applications (Porcine Proliferative Enteropathy). The applicant comments that there have also been no reports of suspected lack of efficacy in the last 5 years.

In the field trials, Econor premix was administered in meal, pelleted feeds and liquid feed including whey. Feed was given *ad libitum* or twice daily, and the outcome of the studies did not appear to be affected by feed type or frequency of feeding. Therefore, although thorough mixing of the oral powder should be ensured to maintain palatability, it appears that the pharmacokinetic profile and homogeneity through the feed are not critical to achieving efficacy, providing the daily dose is consumed.

As the oral powder formulation will essentially be bioequivalent to the premix under conditions of field use, it is acceptable to extrapolate the indications and dose regimen from the Econor premix.

Overall conclusion on efficacy

As it can be considered that the oral powder and premix formulations will essentially be bioequivalent under conditions of field use, the indications, dose regimen and safety warnings supported by the data presented for the premix can be extrapolated to the oral powder formulation.

There is evidence of emergence of valnemulin-resistant strains of *Brachyspira spp*. since valnemulin was first approved for use in pigs. This has been addressed in the SPC.

Part 5 – Benefit Risk Assessment

Introduction

Econor 10% oral powder for pigs contains the active substance, valnemulin. This extension application introduces a new pharmaceutical form, oral powder, to the approved range of Econor products. The Econor oral powder is the same formulation as the 10% premix and the proposed indications and associated dose regimens for the oral powder are already included in the approved SPC for the premix formulation.

Benefit assessment

Direct therapeutic benefit

The proposed indications for the product are for the treatment (only, i.e. not prevention) of swine dysentery, porcine proliferative enteropathy (ileitis) and enzootic pneumonia in individual pigs.

As the oral powder formulation is identical to the premix, bioavailability is expected to be the same. Evidence from field trials, supported by pharmacovigilance, suggests that efficacy is not influenced by feed type or frequency of feeding.

The availability of an oral powder also means that treatment can be started earlier in the course of disease, before medicated feed could be prepared and delivered to the farm (no disease prevention claim is sought). This will aid animal welfare and containment of disease, especially when there are outbreaks of acute disease.

In addition, as the oral powder is for the treatment of individual pigs, more accurate dosing may be achieved in small groups of animals.

Risk assessment

The product is identical in terms of its formulation, manufacture and control to the currently authorised product Econor 10% premix for medicated feed for pigs and is therefore in compliance with the requirements of relevant EU quality guidelines and European Pharmacopoeia monographs.

The use of this new pharmaceutical form (oral powder) will not increase exposure to the user, the consumer or the environment when compared to the use of the premix range of products, as the same dosage, route of administration, user warnings and withdrawal period are used for this new pharmaceutical form.

As the formulation and bioavailability of Econor oral powder will be the same as the premix under conditions of field use, the proposed contraindications and warnings for the target species are the same as for the premix.

Although the MICs of valnemulin for *L. intracellularis* and *M. hyopneumoniae* appear to have remained stable since Econor was authorised in 1999, the MIC_{90}s for the *Brachyspira spp.* appear to have increased and there is evidence in the applicant's and published studies for the emergence of resistant strains. Literature references indicate that resistance to pleuromutilins can develop in *B. hyopneumoniae* by a chromosomal mutation which results in alteration of the drug-binding site on the bacterial ribosome. MIC data from recent studies suggest that the MIC_{90} for *Brachyspira spp.* have increased since valnemulin was first authorised. Although there have not been reports of suspected lack of efficacy of Econor in PSURs, the presence of a resistant strain may be the cause of treatment failure; therefore it is sensible that the possibility of resistance in this organism should be mentioned in the SPC and

appropriate warnings to minimise the future development of resistance have been added to the SPC and product literature.

The introduction of this new formulation of valnemulin should not, in itself, increase the risk for the development of antimicrobial resistance in the target species or man as the dose regimen and relevant indications are consistent with those of the premix.

Evaluation of the benefit risk balance

The Committee considered that the oral powder formulation is essentially bioequivalent to the premix under conditions of field use, user, consumer and environmental exposure are the same.

As also the proposed indications, dosing regimen and warnings reflect those in the SPC of the already authorised premix formulation, the Committee concluded that the overall benefit-risk balance for Econor including the proposed new pharmaceutical form remains positive.

Conclusion

The overall benefit risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented the CVMP considers that the application for the extension application for an oral powder formulation of Econor is approvable.