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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for the extension of a community marketing authorisation for Econor (EMEA/V/C/000042/X/0039)

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

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Introduction

An application for the extension to the marketing authorisation of Econor has been submitted to the Agency on 4 May 2011 by Novartis Animal Health GmbH Austria in accordance with Regulation (EC) No. 1234/2008.

The CVMP adopted an opinion and CVMP assessment report on 13 June 2013.

On 5 August 2013, the European Commission adopted a Commission Decision for this application.

The already authorised target species for this product is pigs. The new target species for the 10% premix formulation is rabbits, and the indication is for the reduction of mortality during an outbreak of epizootic rabbit enteropathy (ERE). Treatment should be started early in the outbreak, when the first rabbit has been diagnosed with the disease clinically.
As per product information the route of administration is oral via in-feed use, at a dose of 3 mg valnemulin/kg bodyweight (i.e. 35 mg valnemulin/kg feed) over 21 days.

Part 1 - Administrative particulars

At their December 2011 meeting, the CVMP confirmed that, where appropriate, the data requirements in the appropriate CVMP guidelines on Data Requirements for Veterinary Medicinal Products intended for Minor Uses or Minor Species (MUMS) would be applied when assessing the application. MUMS status was granted as rabbits are considered a minor species.

Detailed description of the pharmacovigilance system

The applicant has a system in place that will allow it to fulfil its pharmacovigilance obligations in accordance with the requirements of Directive 2001/82/EC. The applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

A certificate of compliance with the principles of Good Manufacturing Practice for the manufacturer responsible for Batch Release, Novartis Santé Animale S.A. was presented. The qualified person at the site of release of the dosage form has supplied a statement confirming that the active substance is produced in accordance with the CVMP/CHMP guideline on GMP for Active Pharmaceutical Substances.

It was considered that no product-specific GMP inspections are required.

Overall conclusions on administrative particulars

It was appropriate to consider this application on the basis of MUMS status and reduced data requirements apply.

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are considered in line with legal requirements.

Part 2 - Quality

The application was to add a new target species for an existing formulation, and the assessment of part 2 of this application therefore focused only on aspects of the product relevant to the use as a premix for medicated feed for rabbits.

No special formulation development studies have been performed to take account of the use of the formulation as a premix for use in rabbit feed. Homogeneity, stability during pelleting and stability during storage of feed were studied using three commercially-available rabbit feeds. The studies were carried out using Econor 10% premix at a concentration of 20 mg/kg valnemulin in the feed. A 20 mg/kg feed concentration was chosen as it represents the most challenging mixing scenario. The mash was pelleted using a pelleting temperature of 75 °C. This corresponds with the SPC statements that "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 premixture should be avoided".

The valnemulin content for the three batches was acceptable for the medicated rabbit feed (mash) as well as for the medicated pellets, in both cases with good homogeneity. There was no significant difference between the content or homogeneity in the mash and in the pellets showing that the pelleting process does not degrade the active substance.

The results obtained during stability study for three batches showed that the active substance is stable for 4 weeks in rabbit pellets at 25 °C/60% RH. Beyond four weeks of storage there was a significant drop in the valnemulin content in all batches.

Based on these data, a shelf-life of 4 weeks was applied to medicated rabbit feed containing Econor 10% premix and the statements in the SPC remain appropriate.

The analytical methods used for the determination of the active substance, valnemulin hydrochloride in rabbit feed were validated.

Overall conclusions on quality

Part 2 has already previously been assessed. Additional, new experiments have been performed to study homogeneity, stability during pelleting and stability during storage in commercial feed prepared using Econor 10% premix. Results are satisfactory.

Based on these data, a shelf-life of 4 weeks can be applied to medicated rabbit feed containing Econor 10% premix and the statements in the SPC remain appropriate.

Part 3 – Safety

This is an extension application to add rabbits to the existing authorisation for pigs. Data relating to the pharmacology, pharmacokinetics, toxicology and studies of other effects of valnemulin have already been assessed by the CVMP during the evaluation for the establishment of MRLs for valnemulin and the centralised authorisation for Econor for pigs. These data are all relevant to this application and cross-reference is made to the reports already accepted for the Econor range of products.

User safety

The products are incorporated into rabbit feed which then has to be pelleted, and is distributed to rabbit farms for use as a mass medication. For use in epizootic rabbit enteropathy (ERE), a daily dose of 3 mg valnemulin/kg bw is given for up to 21 consecutive days. Typically, the product is incorporated

into rabbit feed at a rate of 35 mg/kg feed mg valnemulin/kg feed. For comparison, the maximum dose recommended for pigs is 12 mg valnemulin/kg bw per day for up to 21 days.

Two types of operators were identified, mill workers (mixing the product into rabbit feed) and rabbit farmers (administering the medicated feed to rabbits). The feed mixing procedures are the same as those used for pigs and are conducted at specialist feed mills where workers wear protective equipment. It is considered that exposure of valnemulin to feed mill workers is negligible and certainly not higher than would be expected when mixing these products for pig feed. Since medicated rabbit feed has to be pelleted (rabbits will eat only pellets), valnemulin hydrochloride is encased within the feed pellet and cannot be dislodged. Additionally, on most rabbit farms, the medicated feed is automatically distributed from a central storage silo to the rabbit cages by pipes, without the need to manually handle the feed. The only potential routes of exposure on farm will be to skin, eyes and airways, and by mouth resulting from accidental spillage of medicated feed.

The exposure scenarios were considered to be similar to the use of the product in pigs and no suspected adverse reactions were reported from the use of the product in pigs.

Noting appropriate user safety statements in the product literature, CVMP concluded that the product, when used in accordance with label recommendations, will not pose an unacceptable risk to the user. However in light of the extension of the indications to a new target species it is recommended to re-start the periodic safety update report (PSUR) cycle to ensure more frequent pharmacovigilance monitoring.

Development of resistance

See part 4.

Environmental risk assessment

An environmental risk assessment (ERA) has been provided. Assessment of environmental risk can stop at Phase I provided that the minor species is reared under similar conditions to the major species, the product is administered by the same route and the total exposure of the environment does not increase. In this case both pigs and rabbits will be raised in housing and the environment will be exposed to valnemulin when manure is spread onto land. Comparison of the PEC_{soil} values for fattening pigs (PEC_{soil} 1485 µg/kg) and rabbits (PEC_{soil} 454 µg/kg) demonstrate that the total exposure from the use in rabbits is not greater than exposure from use in pigs. Therefore, no additional data have been provided with this application.

In conclusion, the assessment of environmental risk can end at Phase I based on the fact that the product is for a minor species , andan acceptable ERA already exists, based on its use in the major species, pigs.

It can be concluded that the product will not pose an unacceptable risk for the environment when used in accordance with the recommendations included in the SPC.

Overall conclusions on the safety documentation

The product is not expected to pose a risk for the user or the environment when used as recommended.

Residues documentation

This application is to extend the indication of Econor 10% premix and reduce mortality caused by epizootic enteropathy in farmed rabbits. The proposed in-feed dosing regime for rabbits is 3 mg/kg bw

per day for up to 21 consecutive days. Typically this dose is achieved by mixing into feed at a concentration of 35 mg valnemulin/kg feed. Reference is made to the data submitted for the establishment of valnemulin Maximum Residue Limit (MRL) in rabbits. Relevant sections from the European Public MRL Assessment Report (EPMAR) for valnemulin for rabbits (EMA/CVMP/137196/2009) are re-presented below for ease of reference.

Identification of the product concerned

Econor 10% premix for medicated feed contains 10 mg/g valnemulin as active substance, and silica colloidal anhydrous, isopropyl myristate, hypromellose, talc and lactose monohydrate as excipients.

In residue depletion study in rabbits the Econor 1% premix for medicated feed for pigs was used. This is the formulation described in the original submission for Econor from 2005.

Pharmacokinetics

No radio-labelled metabolism studies were conducted in rabbits. However, as absorption, distribution and elimination were very similar in rats, dogs and pigs, it is reasonable to assume that they would be similar in rabbits. This assumption is supported by the results of an *ex-vivo* study which compared pig and rabbit liver metabolic profiles. In this study, livers from treated pigs and rabbits were extracted with methanol and the extracts were analysed by LC-MS/MS. Valnemulin, the predominant residue, was positively identified, confirming its suitability as the marker residue in rabbits. New Zealand white rabbits (9 - 11 weeks of age), housed individually in an indoor animal facility were treated with valnemulin in medicated feed for 35 consecutive days. The target dose level of valnemulin was 60 mg/kg feed. The overall valnemulin intake per kg bw for each rabbit was approximately 3 mg/kg bw/day. The overall valnemulin intake was slightly higher in female rabbits compared to male rabbits. Liver, whole kidneys and muscle were collected and analysed for valnemulin, using a validated HPLC method. At 0 h post-application, no valnemulin residues were detected in liver, kidney and muscle samples.

Depletion of residues

New Zealand white rabbits (9 - 11 weeks of age), housed individually in an indoor animal facility were treated with valnemulin in medicated feed for 35 consecutive days (Econor 1% premix). The target dose level of valnemulin was 60 mg/kg feed. The overall valnemulin intake per kg bw for each rabbit was approximately 3 mg/kg bw/day. Incorporation of the test item into rabbit feed was completed in a commercial feed mill in two batches 3 weeks apart. The prepared feed was pelleted, sub-sampled and packaged into 25 kg bags. Sub-samples of prepared feed were analysed for valnemulin content. Once prepared, feed bags were stored in the freezer.

Animals were slaughtered at 0, 24 and 48 h following last administration. Tissue samples were then analysed for residues. Valnemulin levels in all tissues were below the LOQ (25 µg/kg) from the first time point (0 hours). Samples from subsequent time points were not analysed with the exception of liver. Liver samples from the 'zero withdrawal' time point were reanalysed to confirm the original results. In addition, the liver samples collected at the 24 h withdrawal time were also analysed and confirmed the results. As discussed in the quality part, the results of the studies with Econor 1% are also considered valid for Econor 10% premix since the formulations are very similar and the concentration of the active substance in the final feed is the same. Given the nature of the product (premix for medicated feedingstuff) and the way it is administered (orally), the results of the study can be used in setting the meat withdrawal period of rabbits.

MRLs

The following constituents of Econor are included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Valnemulin	Valnemulin	Rabbit	50 µg/kg 500 µg/kg 100 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-infectious agents/Antibiotics

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required, or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this veterinary medicinal product.

Withdrawal periods

The residue depletion study detailed above supports a zero day meat withdrawal period for rabbits.

The following text is proposed for inclusion in section 4.11 of the SPC:

'Meat and offal: zero days'.

Analytical methods

The analytical method to detect the marker residue was accepted for rabbits during the setting of MRLs for rabbits.

Overall conclusions on the residues documentation

The residue depletion study supports a zero day meat withdrawal period for rabbits to ensure consumer safety.

Overall conclusions on safety

On the basis of the data provided, the product, when used in accordance with label recommendations, will not pose an unacceptable risk to the user and will not pose an unacceptable risk for the environment. However, in light of the extension of the indications to a new target species it is recommended to re-start the periodic safety update report (PSUR) cycle to ensure more frequent pharmacovigilance monitoring. Taking into account the current PSUR periodicity for the product, to ensure that there are no gaps between submission of PSURs the MAH is requested to submit a PSUR covering the period 01.10.2011 - 30.09.2013, after which the PSUR cycle restart will come into effect and submission of 6-monthly PSURs will commence. The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31.03.2014.

The residue depletion study supports a zero day meat withdrawal period for rabbits to ensure consumer safety.

Part 4 – Efficacy

Introduction

A body of literature has been presented to support the rationale for the use of valnemulin to treat epizootic rabbit enteropathy (ERE). It has been proposed that an unknown aetiological agent causes an imbalance of caecal microbiota and overgrowth of toxin-producing clostridia causing caecal and intestinal paralysis that results in typical ERE. One study examined the role of bacteria in ERE, but did not conclude precisely which bacteria were involved. Another study involving over four hundred SPF rabbits indicated that while the aetiological agent could not be precisely identified, inoculums from infected rabbits would be infectious to other rabbits as early as 2 days after the onset of clinical signs. Two bacterial strains, *C. perfringens* and non enteropathogenic *E. coli* were frequently isolated in high numbers from rabbits with naturally occurring ERE. *C. perfringens* is considered to be an important associated agent in many ERE cases. The efficacy of antimicrobials (bacitracin) in the treatment of ERE has been explored in preliminary studies.

Pharmacodynamics

Valnemulin is a semi synthetic pleuromutilin. Its mode of action is primarily at the 70S ribosomal subunit, but it has a secondary binding site at the interface of the 30S and 50S ribosomal subunits when the 70S is formed. It also binds to the rRNA in the peptidyl transferase centre. These binding sites prevent elongation of the peptide chain.

The pivotal study (2006) determined that there was fair susceptibility across the EU for *C. perfringens* isolated from rabbits to valnemulin with MIC_{50} of 0.125 µg/ml and MIC_{90} 0.5 µg/ml with a range of 0.031-64 µg/ml. Approximately one half of the samples (51) were provided by the sponsor to the test laboratory. These samples were collected in France and Spain from commercial rabbit producers at the time of disease outbreaks. It was not possible to determine whether treatment had been started or not due to the rapid onset of disease and therefore rapid initiation of treatment. Only 17 isolates of *C. perfringens* were obtained from these samples, indicating that this pathogen is contributory to the disease but cannot be considered pivotal. The laboratory was able to obtain more pure isolates from faecal samples taken from ERE outbreaks in France, Spain and Italy. The study also showed a bimodal MIC distribution and a resistant population (MIC >64 µg/ml) with cross resistance to tiamulin.

Development of resistance

Mechanism

The genetic basis for a method of resistance to tiamulin in *E. coli* was described. It is important to note that the study concluded that the tiamulin determinants for resistance do not reside on plasmids, but were a result of point mutation of the gene encoding ribosomal protein L3, preventing tiamulin binding at the peptidyl transferase centre. As valnemulin falls into the same antimicrobial class as tiamulin, it seems probable that there may be a similar mechanism of resistance.

Resistance in target pathogens

As indicated in the section on pharmacodynamics, it is apparent that resistance may develop in *C. perfringens* isolates from rabbits and that there is cross-resistance with tiamulin. Furthermore, in the applicant's field study it is noted that C. perfringens was isolated from rabbits that were necropsied during the treatment period to corroborate the diagnosis of ERE and MIC determination was not conducted. There appears to be little correlation between levels of
C. perfringens in the caecum and incidence of disease. Currently the levels of resistance to valnemulin

in *C. perfringens* are low; this will increase with use of the product. The product should be used at the correct dose rate and for the correct duration with treatment initiated at the correct time instead of being used as a prophylactic treatment.

Pleuromutilins are regarded by the CVMP as critically important antimicrobials in veterinary medicine as they are the sole therapy for some conditions e.g. macrolide resistant *Brachyspira hyodysenteriae* in swine. However, it seems unlikely that use of valnemulin in rabbits might have significant implications for resistance development in pathogens of relevance to other domestic animal species.

Resistance in zoonotic and commensal bacteria

The applicant has re-submitted the expert report that was provided previously in the submission for Econor 10% oral powder for pigs. Although no separate report for rabbits was provided, the Committee considered that the additional risk level for development of antimicrobial resistance of relevance to public health associated with use of the product in the new target species would be negligible.

Pharmacokinetics

The applicant has not presented any classical pharmacokinetics studies to investigate the blood level PK parameters following administration of Econor when administered in the feed to rabbits. The two studies presented for the target species indicate that valnemulin is metabolised by oxidative pathways in the liver and that the total concentration of valnemulin achieved at the site of action in the caecum is likely to exceed the MIC for *C. perfringens* during treatment, although the free ("active") concentration has not been determined.

In part 4 of the dossier, the purpose of PK studies is to support the dose finding, target species safety and clinical studies. This is a MUMS application and in accordance with the CVMP Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/V/CVMP/EWP/117899/2004), interspecies extrapolation of pre-clinical data can be accepted whenever scientifically justifiable. Parts of the data on ADME can be satisfactorily extrapolated from that already provided for laboratory species and pigs. The applicant has not provided a PK/PD analysis for valnemulin/*C. perfringens*. However, it is assumed that although *C. perfringens* has a role to play in the disease it cannot yet be definitively described as the causative pathogen. A PK/PD analysis is therefore not considered relevant for this disease.

Dose determination / justification

The pre-clinical study (2006) indicated that there was susceptibility across the EU for *C. perfringens* isolated from rabbits for valnemulin with MIC_{90} 0.5 µg/ml. Levels of valnemulin in rabbit caecal contents reached 2555-4555 ng/g when rabbits were fed Econor premix 1% for 35 days at a target dose of 60 mg/kg feed . This translates to a minimum caecal concentration of 2.55 µg/g of caecal content. The free ("active") proportion of this is unknown; however, it was reasonable to assume that caecal concentrations in excess of reported MIC values are likely to be achieved in the field when the product is used as recommended.

The (non-GLP) pivotal dose titration pilot study examined prophylactic use of valnemulin, with experimental challenge after four days on medicated feed at three different dose levels, 20 mg/kg feed, 35 mg/kg feed and 60 mg/kg feed. Medicated feed continued to be administered to these groups for a further 14 days (18 days total). This was a one centre randomised trial versus placebo (not blinded), with two different control groups – one unchallenged with ERE and unmedicated, and one challenged with ERE but unmedicated. Each group included 42 rabbits (equal genders).

The unchallenged/unmedicated group received 500 µl of SPF rabbit caecum content *per os* on day 0. The remainder of the groups received 500 µl of intestinal contents of rabbits affected by ERE by the same route at the same time point. Characterisation of the ERE inoculum showed dominance of Gram positive bacteria including *C. perfringens*. *C. spiriforme* and coliforms were not present.

The primary efficacy parameter was effect on weight gain. Secondary efficacy parameters were occurrence of clinical signs of ERE, in particular diarrhoea, bodyweight, mortality and post mortem lesions. Safety parameters measured were daily clinical examination and evaluation of feed consumption.

Clinical signs of ERE only occurred in the challenged untreated group, with a mortality of about 20%.

The primary end point - daily weight gain - was 41.6 g/day, 42.1 g/day and 40.1 g/day in challenged groups treated with 20 mg/kg feed, 35 mg/kg feed and 60 mg/kg feed, respectively. This compared to 47.1 g/day in the unchallenged, unmedicated group and 35.0 g/day in the challenged, unmedicated group. There were 4 deaths (related to ERE) in the unmedicated, challenged group and one death (not related to ERE) in the challenged group receiving 35 mg/kg feed medication.

There was a significant difference in the weight gain for the 20 and 35 mg/kg feed groups, but not the 60 mg/kg feed group, compared to the unmedicated challenge group.

Compared to the unmedicated unchallenged group, weight gains were lower in all medicated challenged groups, and statistically lower in the 20 and 60 mg/kg feed groups. Feed consumption was also lower in these groups. This did not appear to be associated with palatability of the medicated feed, as demonstrated in the period when medicated feed was provided prior to challenge. It is not possible to determine if it may have been due to subclinical ERE or adverse effects associated with valnemulin such as microflora disturbances.

Medication prevented overt clinical manifestation of ERE in terms of mortalities in all treated groups compared to the untreated challenged group. Weight gains were highest in the 35 mg/kg feed group, although there was no clear dose-effect relationship.

In conclusion, although a treatment benefit was demonstrated in terms of weight gain and decreased mortality for valnemulin when administered prophylactically, there was no clear dose-response relationship in this study. There were also many shortcomings in the study design (lack of medicated unchallenged control group, non-standardised inocula, prophylactic use). It was seen in this study that rabbits were continuing to die after 14 days of treatment whether treated with valnemulin or not and literature references have reported mortality continuing for 2.5 weeks in untreated controls. This indicated that a longer treatment duration was necessary. Dose confirmation in the field supported a treatment duration of 21 days (see clinical part). Treatment should be combined with biosecurity measures and control of husbandry factors.

The actual mg/kg dose rates for this study were not calculated, but from earlier laboratory studies it was concluded that the doses were approximately 1.56-1.81 mg/kg/day (20 mg/kg feed) and 2.61-3.42 mg/kg/day (35 mg/kg feed). As the 60 mg/kg feed group had demonstrated a higher mortality this dose was not tested further. In the remaining two treated groups (20 and 35 mg/kg feed), rabbits showed significant benefits compared to the untreated control group, with greater benefits seen in the 35 mg/kg feed group. The 20 and 35 mg/kg feed inclusion rates were taken forward to the clinical studies.

Target animal tolerance

A GLP preliminary dose range finding study was conducted in rabbits dosing by oral gavage at either 150 mg/kg (group 1) or 31.25 mg/kg (group 2) valnemulin once daily for 5 consecutive days.

However, due to an unacceptable reaction dosing was stopped after 3 days in group 1 and 4 days in group 2. At both dose levels reductions in food consumption, bodyweight and faecal output were seen. It was considered that the effects seen were probably due to interference with gut micro flora and therefore that the toxicity was an indirect effect of treatment, rather than a systemic effect.

In a 10-day pilot study involving oral feeding of valnemulin in rabbits , four week old male and female (3 of each sex) rabbits received either 3.7 mg/kg or 16.4 mg/kg valnemulin once daily for 10 days. Results showed that food consumption, bw, organ weights, ophthalmology, and haematological parameters were unaffected by the treatment in either group. Gross pathology showed no macroscopic findings. There were no unscheduled deaths and no adverse clinical signs were noted throughout the study. The CVMP has previously concluded from this study that Econor 1 % premix at daily dose rates of 3.7 (approximately 1x clinical dose) and 16.4 mg/kg (approximately 5 x clinical dose) valnemulin for ten days was well tolerated by rabbits.

Residues of valnemulin were examined in edible tissues following continuous administration of Econor premix 1% in feed at 60 mg/kg feed (translated into around 3 mg/kg actual intake) valnemulin for 35 days to rabbits. All animals survived to scheduled necropsy. No abnormal clinical signs were noted and the food consumption was comparable between treatment and control groups. Bodyweights between groups were also comparable and no notable differences were recorded in renal fat, liver or kidney weights. There were no macroscopically abnormal findings at necropsy in any animal.

In the dose titration study (2008) ERE-challenged animals received either valnemulin at three different dose levels (20 mg/kg feed, 35 mg/kg feed, 60 mg/kg feed, corresponding to a daily dose of up to 1.8, 3.4 and 5.6 mg/kg bw) or unmedicated feed ad libitum for 18 days. All animals were daily checked for clinical signs and impact on bodyweight and feed consumption.

The cause of death of one rabbit in the 35 mg/kg feed group could not be determined conclusively from the clinical signs and necropsy findings. Daily weight gain was lower in the challenged rabbits as compared to unchallenged placebo (47 g/day) but still higher in the treated (41.6, 42.1, 40.1 g/day) than in the untreated, challenged group (35 g/day). One rabbit in the 60 mg/kg feed group showed slight diarrhoea on Day 7, but made a good recovery. Otherwise there were no adverse events reported in the medicated groups.

As the incidence of mortality in the medicated rabbits was very low, and there was no apparent relationship of the single death with the dose, the CVMP did not consider that this case could be considered as evidence of direct toxicity of valnemulin. It is noted that in this study SPF rabbits, free of *Clostridium spiroforme* were used. This organism has been implicated as a cause of enterotoxaemia which is associated with indirect antibiotic toxicity resulting from disruption of the intestinal flora following administration of antibiotics to rabbits. The risk of indirect toxicity therefore could not be fully assessed in the study.

The first field study was performed on a commercial rabbit farm in the face of a natural outbreak of ERE in 553 rabbits 43 days old and groups received valnemulin in feed at either 0, 20, 35 or 60 mg/kg feed for 21 days. Parameters studied were mortality, weight gain, and clinical signs of ERE. Overall, the incidence of adverse events in the treated groups compared to the untreated group was comparable. *E coli* enteritis occurred in 2 out of 415 treated rabbits compared to 2 out of 138 unmedicated rabbits. Hepatopathy, which was “possibly” treatment related, occurred in 1 out of 415 (0.24%) of treated rabbits and none out of 138 unmedicated rabbits.

There were no clearly apparent adverse events (not attributed to ERE) reported in the 60 mg/kg feed group. “All-cause” mortality rates were higher in this study in the 60 mg/kg feed dose group compared to the 20 and 35 mg/kg feed dose groups (23.5%, 17.9% & 18%, respectively), and very similar to

that in the negative control group (23.3%). Any adverse events due to treatment may be have been obscured by the presence of ERE disease. It should be noted that the differences in weight gain between groups were not statistically significant, and data are therefore inconclusive, however the numerical difference in all-cause mortality for the 60 mg/kg feed group compared to the negative control was negligible. Consequently the concern about the margin for safety remains as any potential benefit from treatment might be negated by a small overdose.

During a second clinical study, a total of 23 adverse events (pneumonia, enterotoxaemia, dysbacteriosis, coccidiosis) in 23 rabbits were reported, all of which were considered serious. These events included 11 reports from rabbits treated at 20 mg/kg feed Econor (2.9%), 5 reports from those that received 35 mg/kg feed Econor (1.3%), and 7 reports from the untreated group (1.6%). The outcome of all adverse events was death, and the diagnosis was confirmed on post-mortem examination. No statistically significant differences either in the overall adverse event incidence or in the frequency of the reported adverse event types between groups were observed. All adverse events were deemed unrelated to treatment and the incidence was within normal rates for rabbits which have been weaned and regrouped on this farm.

Clinical signs representative of ERE (borborygmus, tympanism, impaction and diarrhoea) were recorded on a daily basis. Every animal presenting at least one of these clinical signs was followed-up until it either recovered or died.

Of 308 animals that presented ERE signs, 146 recovered for a successful outcome and 159 died (ERE diagnosis confirmed post-mortem). The percentage of animals that presented at least one ERE clinical sign was remarkably similar in all three treatment groups (89, 112 and 105; 23.5%, 29.5% and 27.4% of 383 animals included in each treatment group respectively). However, mortality within clinically affected animals was 46.7%, 25.7% and 83.3%, in animals that received 20 mg/kg feed, 35 mg/kg feed of Econor or were untreated, indicating that although treatment with Econor had an influence on the severity of the disease and its outcome (significant decrease in mortality rate), a similar number of animals will be showing at least one clinical sign indicative of ERE.

Removal rates for all-cause mortality (due to ERE or adverse events) were 24.5%, 13.8% and 8.9% in control group, 20 mg/kg feed and 35 mg/kg feed Econor groups respectively. Differences between any 2 groups were statistically significant (all-cause mortality inversely correlated with valnemulin concentration in the feed).

In this study, the administration of valnemulin hydrochloride did not negatively affect feed consumption or body weight gain, did not result in an increase in the overall incidence of adverse events, nor of adverse events that could be indicative of an antimicrobial effect on the gastrointestinal flora. Even though administration of valnemulin resulted in a higher frequency of tympanism, this could not be correlated with a negative outcome of the disease. Therefore, it can be concluded that the administration of valnemulin premix in feed at concentrations of 20 and 35 mg/kg feed for 21 days is well tolerated under field conditions during an outbreak of ERE.

In summary, the data submitted in support of target animal safety were in line with CVMP guidance on requirements for minor species and it has been established that an inclusion rate of 35 mg/kg feed for up to 21 days is tolerated by rabbits. Due to concerns that at inclusion rates of 60 mg/kg feed, daily weight gain may be adversely affected (which may be indicative of damage to gastrointestinal flora), a warning was included in the SPC stating that the product should not be overdosed due to the risk of enterotoxaemia.

Field trials

In total, two GCP field trials were submitted in support of this application.

The first field trial was conducted in 2011 on a single commercial rabbit farm in Spain with a history of naturally occurring ERE, during a confirmed outbreak. It was a randomised, blinded, placebo controlled field trial with three valnemulin (Econor 10 mg/g premix) treatment groups and an unmedicated control group as follows: 20 mg/kg feed (target 1.56-1.81 mg/kg bw/day), 35 mg/kg feed (target 2.61-3.42 mg/kg bw/day), 60 mg/kg feed (target 4.02-5.55 mg/kg bw/day), and placebo (non-medicated feed); administered orally daily in pelleted feed for 21 consecutive days to the relevant groups. In total, 553 New Zealand x California weaned rabbits aged 48 days at D0 were enrolled (136 to 140 animals/group).

The primary efficacy variable was defined as the percentage of animals that died from ERE during the study. The secondary efficacy variables were mean body weight, average daily weight gain, average daily feed consumption and clinical signs of ERE. In order to clarify the effect of the treatment (valnemulin, Econor premix) in animals in the early stage of the ERE outbreak, an additional statistical analysis was conducted in which only results from animals with no clinical signs of disease (ERE) on Day 0 were included.

At the start of the outbreak and prior to treatment, ERE was confirmed by necropsy in 13 of 17 rabbits that died; 32.5% of these rabbits had been affected with clinical signs of ERE (borbroygmus). *C. perfringens* (the model used for preclinical development of this proposed indication) was only identified in 2 of 10 samples taken from the necropsied rabbits. It is acknowledged that the precise aetiology of ERE remains to be elucidated.

For the primary efficacy variable (% mortality related to ERE (D0 to 28)), rates were numerically lower in 20 mg/kg feed (22/137, 16.1%) and 35 mg/kg feed (24/138, 17.4%), and higher in 60 mg/kg feed (32/136, 23.5%) compared with placebo (30/136, 22.1%). There was no statistically significant difference in percentage of mortality related to ERE between treated groups and negative control (Chi-Square Test $p=0.3413$, Cochran Armitage Trend Test $p=0.1243$; Fischer's exact test and a logistic regression model).

There was no statistically significant difference per treatment group for any of the secondary variables measured (mean body weight, average daily weight gain, average daily feed consumption and clinical signs of ERE). Mortality after D15 was dramatically reduced in all groups (including the control) therefore the need for a third week of treatment was considered questionable based on the results of this study.

The additional sub group analysis performed on rabbits not demonstrating any signs of ERE on day 0 showed a numerically lower mortality related to ERE for animals in the 20 mg/kg feed and 35 mg/kg feed groups (mortality 6.1% and 6.2%, respectively) compared with animals in the 60 mg/kg feed group (12.3%) and placebo animals (13.5%). These differences were not statistically significant ($p=0.2344$).

This field study failed to demonstrate a statistically significant treatment benefit as measured by reduction in mortality, weight gain, feed consumption and clinical signs for any of the treatment dose levels. In numerical terms, the best performing group (20 mg/kg feed) showed a 6% reduction in mortality compared to the unmedicated group. The "additional analysis" of animals that were healthy at D0 (metaphylaxis) showed a 7.4% reduction in mortality for the best performing group (20 mg/kg feed) which was also not statistically significant. "All-cause" mortality rates were higher in the 60 mg/kg feed dose group compared to the 20 and 35 mg/kg feed dose groups (23.5%, 17.9% and 18%,

respectively), and very similar to that in the negative control group (23.3%). It is possible that adverse events related to treatment could have been obscured by the presence of ERE disease.

As the results of this field study were inconclusive, further field data were required to generate statistically and clinically robust results.

A second GCP-compliant clinical study was conducted in 2012 on a commercial rabbit farm in Hungary, which had a history of previous outbreaks of ERE. This too was a randomised, blinded, placebo controlled study to evaluate the efficacy and safety of Econor premix administered orally daily in feed for 21 consecutive days in the treatment and prevention of naturally occurring epizootic rabbit enteropathy (ERE). The study was conducted in line with scientific advice from CVMP and incorporated an earlier onset of treatment than the previous study. The trial treatment was initiated after the first rabbit showed clinical signs and the diagnosis was confirmed by post-mortem examination.

After weaning, at the age of about 35 days (body weight 755-1025 g), Hycole hybrid rabbits were delivered to the farm from the breeding station. Three rows of commercial rabbit fattening cages containing 96 cages (four rabbits per cage) were randomised to one of three treatment groups. In total, 1152 rabbits were initially included. They were of normal physical condition with no concurrent disease. Three rabbits were excluded from the study before treatment start due to ERE outbreak or adverse events. The remaining 1149 animals were retained, allocated to three different treatment groups of 383 rabbits each; 0, 20 and 35 mg valnemulin/kg feed. The rabbits were treated for 21 consecutive days, starting immediately after the onset of disease on the farm. The medication was mixed in feed, which was offered ad libitum to the rabbits. The feed for all groups also contained robenidine as a coccidiostat, as common good farming practice recommends. The product is not expected to interfere with the evaluation of efficacy and safety of the test treatment.

Animals were observed daily for general health and clinically examined including recording bodyweight at the end of each week.

The primary efficacy variable was '% mortality' (animals dying/euthanased as a result of ERE outbreak during the study between days 0-28 in each treatment group). All animals found dead or euthanised as a result of severe disease were necropsied by the investigator to establish cause of death and whether or not the mortality was caused by ERE, based on the evaluation of the presence or absence of the following macroscopic parameters: overfilled stomach, overfilled small intestine, caecal impaction, presence of mucous in the colon, presence of mucous in the small intestine.

Secondary clinical efficacy endpoints were presence or absence of borborygmus, tympanism, impaction and diarrhoea observed during individual clinical observations. The secondary efficacy variables were mean bodyweight, average daily weight gain, average daily feed consumption per cage and clinical signs of ERE. Average daily weight gains were calculated over periods throughout the study and compared. Average daily feed consumption per cage was calculated over the entire observation period (day -1-28).

Treatment was stopped on day 21 and the final examination was performed on day 28.

Results:

Mortality due to ERE was 11.0% for 20 mg/kg feed (42/383 rabbits), 7.6% for 35 mg/kg feed (29/383 rabbits) and 23.0% (88/383 rabbits) for the untreated control group. The differences between each of the treated groups (20 and 35 mg/kg feed) compared to the untreated control group were statistically significant ($p=0.0001$). No statistically significant difference was seen between the lower and higher dose rates of Econor ($p=0.1344$).

Differences in body weight gain remained non-significant throughout the study period (D0-28). During the treatment phase, mean daily weight gain was significantly higher in treated animals than controls (p=0.0389). Taking the uncorrected body weight increases on days 7, 14 and 28, the differences between groups were not statistically significant. This provides reassurance that the product is unlikely to be used as a growth promoter. The average daily feed consumption per cage throughout the whole study period was significantly different between all treatment groups (477.9 g/day for the untreated group compared to 572.6 g/day for the group treated with 35 mg/kg feed), although this may have been due to the higher mortality in the control group cages.

A total of 23 adverse events were reported (out of 1149 rabbits). It appears that the frequency of adverse events in each group (such as dysbacteriosis due to *E.coli*, enterotoxaemia, coccidia infection and *Pasteurella pneumoniae*) was consistent with mortality rates usually encountered on the farm for weaned and mixed rabbits. The incidence was not statistically significantly different between all 3 groups.

A total of 306 rabbits presented with signs of ERE, and of those, approximately 50% died and 50% recovered. The proportion of rabbits that presented with at least one clinical sign of ERE was similar in all 3 groups, however this then only resulted in mortality in 25.7% of affected rabbits treated with 35 mg/kg feed, 46.7% of affected rabbits treated with 25 mg/kg feed compared with 83.3% of affected untreated rabbits.

Rabbits treated with valnemulin premix had a lower frequency of impaction and diarrhoea than the control group. Impaction appeared to be more frequently observed in rabbits that died, independently of whether they were treated with valnemulin or not. Tympanism was more frequently reported among rabbits that were treated with valnemulin compared to the control group. A large proportion of the tympanic cases occurred in rabbits that recovered (53 rabbits in 20 mg/kg feed group and 85 in 35 mg/kg feed group) indicting that tympanism did not correlate with a negative outcome. The number of rabbits affected with diarrhoea was similar in treated and untreated rabbits, independent of the outcome of the disease, with an overall higher count of diarrhoea cases in the untreated group.

Removal rates for all-cause mortality (due to ERE or adverse events) were 24.5%, 13.8% and 8.9% in control group, 20 mg/kg feed and 35 mg/kg feed Econor groups, respectively. Differences between any 2 groups were statistically significant (all-cause mortality inversely correlated with valnemulin concentration in the feed).

Although there was no statistically significant difference in mortality between the treated groups, the data overall show that the inclusion rate of 35 mg/kg feed appears to be more beneficial than the lower dose rate of 20 mg/kg feed. Given that sick rabbits have a variable intake of food, a higher inclusion rate is preferable and 35 mg/kg feed (equating to 3 mg/kg bodyweight/day) was confirmed for the posology.

The overall conclusions from this pivotal second field study were that while valnemulin cannot prevent the disease from becoming clinically manifested, it had a positive and clinically relevant effect in terms of reducing the severity of disease and improving its outcome. Valnemulin has been shown to be safe and efficacious in the reduction of mortality when treatment is instigated early in an outbreak of ERE.

Overall conclusion on efficacy

The aetiology for ERE remains to be fully elucidated; however, *C. perfringens* appears to play a role in the aetiology of the disease, although it is not considered to be the definitive pathogen responsible for the disease. There is generally good susceptibility across the EU for *C. perfringens* isolated from cases

of ERE to valnemulin with MIC_{50} of 0.125 µg/ml and MIC_{90} 0.5 µg/ml (range 0.031-64 µg/ml), although cross-resistance to tiamulin appears to exist.

The proposed therapeutic dose of 35 mg valnemulin/kg feed for up to 21 days was well tolerated by rabbits. Although no target animal safety study in line with VICH GL 43 was provided, tolerance was sufficiently demonstrated by pre-clinical and clinical data, and this approach was considered to be in line with MUMS guideline requirements. Higher inclusion rates (60 mg/kg feed) indicated that that daily weight gain may be adversely affected, which may be indicative of damage to gastrointestinal flora. Therefore a warning was included in the SPC stating that the product should not be overdosed due to the risk of enterotoxaemia.

A dose determination study investigated valnemulin doses of 20, 35 and 60 mg/kg feed administered for 18 days from 4 days prior to challenge with an ERE inoculum. In regards to the endpoints of weight gain and mortality, a statistically significant and clinically relevant treatment benefit was shown at all dose levels and there was no clear dose response relationship. Taking into consideration adverse reactions seen in the highest dose (60 mg/kg feed), a dose between 20-35 mg/kg feed was considered optimal for efficacy. From earlier laboratory studies, it was concluded that inclusion rates of 20 and 35 mg valnemulin/kg feed are approximately 1.6-1.8 mg/kg bw/day (20 mg/kg feed) and 2.6-3.4 mg/kg bw/day (35 mg/kg feed), respectively. This was confirmed by a clinical study, where the inclusion rate of 35 mg/kg/feed was approximately 3 mg/kg bw/day.

In support of efficacy, the applicant presented two field studies.

The first was a well conducted GCP field trial conducted in Spain, investigating the efficacy of three doses of valnemulin in the treatment of a natural outbreak of ERE (20, 35 and 60 mg/kg feed). However, study results were inconclusive and further field data were required to generate statistically and clinically robust results.

The second clinical trial was conducted in Hungary (2012) to evaluate the efficacy and safety of Econor premix (20 and 35 mg valnemulin/kg feed) administered orally daily in feed for 21 consecutive days in the treatment and prevention of naturally occurring ERE. The study was conducted in line with scientific advice from CVMP. Valnemulin treatment showed a statistically significant effect versus placebo, on the severity of disease and its outcome (reduction in mortality rate) although it does not prevent the disease from becoming clinically manifested. The inclusion rate of 35 mg/kg feed appeared to be more beneficial than the lower dose rate of 20 mg/kg feed. Taking into account that sick rabbits have a variable intake of food, a higher inclusion rate, if shown to be safe, is preferable. Therefore, the CVMP agrees that 35 mg/kg feed (corresponding to 3 mg/kg bodyweight/day) should be the recommended inclusion rate.

Taking the results of the study and other data presented into account, the following indication was agreed by CVMP: “Reduction of mortality during an outbreak of epizootic rabbit enteropathy. Treatment should be started early in the outbreak; when the first rabbit has been diagnosed with the disease clinically”.

Part 5 – Benefit risk assessment

Introduction

This is an extension application for Econor to add rabbits as a new target food producing species to the 10% premix for medicated feedingstuff presentation. Reduced data requirements have been accepted on the basis of a MUMS classification. The product contains valnemulin (100 mg/g) as the active

substance. The product is mixed into rabbit feed at an inclusion rate of 35 mg valnemulin/kg feed (i.e. approximately 3 mg valnemulin/kg bw) and administered over 21 days to rabbits for the reduction of mortality during an outbreak of epizootic rabbit enteropathy (ERE). The withdrawal period for rabbit meat and offal is 0 days.

Benefit assessment

Direct therapeutic benefit

Valnemulin is a well-known semi-synthetic pleuromutilin antibiotic which shows good activity against a range of bacteria, including *C. perfringens, which* play a role in the aetiology of the ERE.

Efficacy of the proposed dose has been demonstrated in clinical and pre-clinical studies in rabbits for the indication: "Reduction of mortality during an outbreak of epizootic rabbit enteropathy (ERE). Treatment should be started early in the outbreak when the first rabbit has been diagnosed with the disease clinically." The product is intended for use in commercial rabbit farms, and the therapeutic benefit would be seen during the post weaning, fattening period, when outbreaks of ERE commonly occur in rabbits, and in particular on farms where the disease is endemic.

The pivotal clinical field trial demonstrated that administration of Econor premix to rabbits for 21 days at an inclusion rate of 35 mg/kg feed (corresponding to 3 mg/kg bodyweight/day) was safe and efficacious during a field disease outbreak of ERE as measured by reduction in mortality, reduction in clinical signs, bodyweight gain and improved feed consumption.

Additional benefits

This application for a premix for medicated feedingstuff provides a convenient way of administering valnemulin to large numbers of rabbits without additional stress placed on animals from handling. The product also provides a new treatment possibility for a minor species.

Risk assessment

The pharmaceutical part has already been assessed previously. Additional experiments have confirmed that homogeneity, stability during pelleting and stability during storage in commercial rabbit feed prepared using Econor 10% premix are satisfactory.

Concerning target animal safety, the main potential adverse reaction associated with the administration of antimicrobials to the rabbit is the disturbance of the gastrointestinal microflora, which ultimately may result in enterotoxaemia. There is clear toxicity for valnemulin at 10x recommended therapeutic dose (RTD), and in a field study, the highest dose rate group (60 mg/kg feed) experienced reduced daily weight gain compared to other treatment groups. The pivotal clinical field trial supports safety of the product at an inclusion rate of 35 mg/kg feed (3 mg/kg bodyweight/day); the risk therefore relates principally to overdose.

An acceptable user risk assessment and Phase I ERA have been provided. The product is not expected to pose a risk for the user or the environment when used as recommended.

A satisfactory residue depletion study has been provided and no residues were detected from zero days after completion of the treatment. Therefore, the product is not expected to pose a risk to consumers when used as recommended, and the withdrawal period of zero days for meat and offal is established.

C. perfringens isolates from cases of ERE within the EU, showed a bimodal distribution towards valnemulin indicating a resistant population. Currently the level of resistance to valnemulin in *C. perfringens* is low; this will probably increase with use of the product. The product should be used at the correct dose rate and for the correct duration with treatment initiated at the correct time (early in the course of disease, but not as a prophylactic treatment). The results of the robust clinical trial support the proposed dose and duration.

Risk management or mitigation measures

An inclusion rate of 35 mg valnemulin/kg feed for up to 21 days is tolerated by rabbits; the risk of enterotoxaemia linked to overdose is highlighted in the SPC.

Suitable warnings related to the prudent use of antimicrobials are incorporated into the SPC, as well as a recommendation that the product should be used as part of a programme including measures aimed at eradicating or controlling the infection on farm.

Taking into consideration that a new target species was added to the existing presentations of Econor and also in view of the reduced data provided for this application, the CVMP recommended re-starting the PSUR cycle to ensure more frequent pharmacovigilance monitoring.

Appropriate advice to users and for disposal is included in the SPC.

Conclusions of the benefit-risk balance

The overall benefit risk balance is considered to be positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of this extension application is considered to be in accordance with the requirements of Directive 2001/82/EC and that the benefit-risk balance of the product remains favourable.