3 September 2010
EMA/CVMP/137196/2009
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Valnemulin (rabbits)

On 24 August 2010 the European Commission adopted a Regulation[1] establishing maximum residue limits for valnemulin in rabbits, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Valnemulin is intended for use in rabbits for the treatment of epizootic rabbit enteropathy by oral administration.

Valnemulin had maximum residue limits already established for porcine species.

Novartis Animal Health submitted the application for the extension of maximum residue limits to the European Medicines Agency (The Agency), on 6 January 2009.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use concluded that the substance should be included in Table 1 of Commission Regulation (EU) 37/2010. Subsequently the Commission recommended on 2 July 2010 that maximum residue limits in rabbits are established. This recommendation was confirmed on 23 July 2010 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 24 August 2010.

Explanatory Note

The European Public MRL Assessment Report is a public document giving the overview of the assessment carried out by the Committee for Medicinal Products for Veterinary Use (CVMP) of an application submitted for the establishment of maximum residue limits (MRLs). The document is based on the CVMP assessment report of the application from which confidential information has been deleted.

Keywords: Valnemulin, rabbits

[1] Commission Regulation (EU) No 758/2010, O.J. L223, of 25.08.2010

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1. Summary of the scientific discussion for the establishment of MRLs

Substance name:	Valnemulin
Procedure number:	EU/09/165/NOV
Applicant:	Novartis Animal Health Inc
Target species:	Rabbits
Intended therapeutic indication:	Treatment of epizootic rabbit enteropathy
Route of administration:	Oral

2. Introduction

Valnemulin is an antibiotic belonging to the pleuromutilin group, which acts by inhibition of bacterial protein synthesis. Its chemical structure is similar to that of tiamulin. Valnemulin is already approved for treatment of bacterial diseases in pigs via oral administration. The approved maximum recommended dose for the treatment of swine enzootic pneumonia is 12 mg valnemulin per kg bodyweight in feed.

Valnemulin has previously been assessed by the CVMP and a microbiological ADI of 477 µg per person per day (i.e. 7.95 µg/kg bw) was established. A toxicological ADI of 4800 µg per person was also established.

Valnemulin is included in Table 1 of Commission Regulation (EU) No 37/2010 in accordance with the following table:

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

An application has now been submitted to extend the MRLs for valnemulin to rabbits. The proposed indication for rabbits is treatment of epizootic rabbit enteropathy. The proposed maximum recommended dose is 4.5 mg valnemulin/kg bodyweight in feed.

3. Scientific risk assessment

3.1. Safety assessment

The CVMP has previously assessed the consumer safety of valnemulin and a microbiological ADI of 477 µg per person per day (i.e. 7.95 µg/kg bw) was established. A toxicological ADI of 4800 µg per person was also established. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application

3.1.1. Overview of toxicology

In the previous evaluation of valnemulin concerning the establishment of maximum residue limits for pigs, the CVMP noted that in a study where rabbits were administered 31.25 or 150 mg/kg of valnemulin per day, severe toxicity was observed, and the study was discontinued after 3 to 4 days.

The toxicity seen in this study may have been related to the fact that the test substance was administered by gavage, which would have resulted in transient high concentrations of valnemulin passing through the gastro-intestinal tract, and which may in turn have caused pronounced local effects, possibly on the gut microflora, rather than being reflective of systemic toxicity.

New data submitted with this extension application included a pilot study in which 3.7 or 16.4 mg/kg bw/day of valnemulin was administered to New Zealand White rabbits in feed for 10 days. Fewer adverse effects were observed in this study, with no mortality, no clinical signs, no ocular alterations, no treatment-related differences in food intake and body weight, no relevant differences in the haematological parameters, no macroscopic alterations at necropsy and no relevant differences in organ weights. Increased serum levels of total protein and albumin, which were observed in females of the high dose group only, were considered to be not clinically significant. The findings of this pilot study, although not yet confirmed in a more comprehensive study, may reflect the lower doses and/or the fact that the test substance was administered in feed.

3.1.2. Findings of EU or international scientific bodies

No MRLs for valnemulin have been established by JECFA/Codex Alimentarius.

3.2. Residues assessment

3.2.1. Pharmacokinetics in target species

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 analyzed 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 bodyweight 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 withdrawal, valnemulin residues in liver, kidney and muscle specimens were not detected.

3.2.2. Residue depletion studies

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 bodyweight 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 withdrawal, valnemulin residues in liver, kidney and muscle specimens were not detected

Valnemulin is considered as the marker residue in rabbits as its presence has been confirmed in rabbit liver. Although no data are available on the ratio of marker to total microbiologically active residues in rabbits, it is expected that this ratio will be similar to that in pigs. The main target tissue in rabbits can

be considered to be liver as it is not expected that rabbits would have a different pharmacokinetic profile from that in rats, dogs and pigs.

3.2.3. Analytical method for monitoring of residues

A validated analytical method for pig tissues was submitted and accepted as the routine method for monitoring residues. The same analytical method is now proposed for routine monitoring of valnemulin residues in rabbit liver, kidney and muscle. A limited validation study of the analytical method in line with the *CVMP Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin* (EMEA/CVMP/187/00-Final) has demonstrated that the method is acceptable for rabbit tissues.

4. Risk management considerations

4.1. Elaboration of MRLs

Considering that the same marker residue and the same ratio of marker to total microbiologically active residues as established for pigs are proposed for rabbits, the MRLs for valnemulin established for porcine tissues (muscle - 50 µg/kg; liver - 500 µg/kg and kidney - 100 µg/kg kg) are now proposed for rabbits also. In addition, when establishing MRLs for pigs the CVMP agreed that as no residues were detectable in fat, no MRL would be required for this tissue; the same approach can now be followed for rabbits.

Calculation of theoretical daily intake of residues

Detailed calculation of theoretical daily intake of residues- table to be included, if applicable

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue*	Amount per edible tissue or product
Muscle	0.30	50	0.85	17.6
Fat	0.05	--	0.85	
Liver	0.1	500	0.85	58.8
Kidney	0.05	100	0.85	5.9
Total (TMDI)				82.3
TMDI as % microbiological ADI (477 µg/person				17.2%

These figures are based on the assumption that the ratio of marker to total microbiologically active residues is similar in rabbits and pigs

Based on these MRLs and the assumed ratio of marker to total microbiologically active residues, it was calculated that the consumer intake of microbiologically active residues would represent approximately 17% of the microbiological ADI. This demonstrates a wide margin of safety even allowing for the fact that the ratio of marker to total microbiologically active residues is based on an assumption.

4.2. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- a microbiological ADI of 477 µg per person was previously established for valnemulin,
- valnemulin was accepted as the marker residue in rabbits,
- the ratio of marker to total microbiologically active residues in rabbits was expected to be similar to that established in pigs (0.85),
- MRLs have been established for the major species porcine, these MRLs are identical to those recommended for rabbits,
- a validated analytical method based on HPLC for the determination of residues of valnemulin in porcine tissues is available and the validation data on rabbits allows to conclude that the method is applicable to rabbit tissues;

the Committee recommends the extension of maximum residue limits for valnemulin to rabbits in accordance with the following table:

Pharmaco-logically 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

5. Background information on the procedure

Submission of the dossier	6 January 2009
Steps taken for assessment of the substance	
Application validated:	16 January 2009
Clock started:	17 January 2009
CVMP opinion adopted:	16 April 2009