MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

VALMUVET 100 mg/g premix for medicated feed for pigs and rabbits

CORREO ELECTRÓNICO
mresvet@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443

PRODUCT SUMMARY

EU procedure number	ES/V/0418/001/DC
Name, strength and pharmaceutical form	VALMUVET 100 mg/g premix for medicated feed for pigs and rabbits
Applicant	VETPHARMA ANIMAL HEALTH, S.L. Gran Via Carles III, 98, 7ª 08028 Barcelona Spain
Active substance(s)	Valnemulin hydrochloride
ATC vetcode	QJ01XQ02
Target species	Pigs, rabbits
Indication for use	Pigs: - Treatment and metaphylaxis of swine dysentery associated with Brachyspira hyodysenteria susceptible to valnemulin. - Treatment of clinical signs of porcine proliferative enteropathy (ileitis) associated with Lawsonia intracellularis susceptible to valnemulin. - Treatment and metaphylaxis of swine enzootic pneumonia associated with Mycoplasma hyopneumoniae susceptible to valnemulin. The presence of the disease in the group must be established before the product is used. Rabbits: 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.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Generic application in accordance with Article 18 of Regulation (EU) 2019/6 as amended.
Reference product (RP)	ECONOR 10% premix for medicated feeding stuff
Marketing authorisation holder	Elanco GmbH
MS where the RP is or has been authorised	
Marketing authorisation number	EU/2/98/010/017
EU procedure number	EMEA/V/C/000042
Date of authorisation	12/03/1999
Date of completion of the original decentralised procedure	21/09/2022

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

The VMP contains 100 mg/g of valnemulin *and* paraffin, light liquid as a lubricant, silicon dioxide E 551, as a flowability power agent and almond hulls as diluent.

The container/closure system is a 25 kg multi-layer paper bag with internal low density polyethylene bag.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

2.B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

The VMP is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

2.C. Production and control of starting materials

The active substance is Valnemulin Hydrochloride, an established active substance described in the European Pharmacopeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this VMP.

2.D. Control tests carried out on isolated intermediates during the manufacturing process

NA

2.E. Control tests on the finished product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification and their limits have been justified and are considered appropriate to adequately control the quality of the VMP.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

2.F. Stability tests

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

2.G. Other information

Appropriate data have been provided regarding the medicated feeding-stuff.

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. Safety tests

Pharmacological studies

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of pharmacological tests are not required.

Toxicological studies

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of toxicological tests are not required.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the candidate formulation will not present an unacceptable risk for the user than the reference product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 2189.6 µg/kg for the weaner pig scenario and 454.36 µg/kg for the rabbit scenario) is greater/equal to 100 µg/kg and no mitigations exist that alter the PECsoil.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	48.18 ± 2.48 g/L	
Dissociation constant	OECD 112	pKa = 7.557 ± 0.035 pKb = 6.443 ± 0.035	
UV-Vis Absorption spectrum	OECD 101	Acidic = 215.5-288.5 nm Neutral = 215.5-288.5 nm	
Melting point	OECD 102	90.1-155 ºC	

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Vapour pressure	OECD 104	Vapour pressure at 20 °C: $1.31x10^{-05}$ Pa Vapour pressure at 25 °C: $2.04x10^{-05}$ Pa	
n-Octanol water partition coefficient	OECD 117 OECD 107	Log Pow = 3.4 Log Pow = 1.924 (20ºC)	

Environmental fate		
Soil Adsorption/Desorption	OECD 106	IME 01-A Koc = 1219.4 IME 02-A: Koc = 3271.0 IME 03-G: Koc = 1712.8 IME 05-G: Koc = 7029.1 IME 06-A: Koc = 3832.3 **Geometric mean Koc = 2837.7 ml/g**
Aerobic and Anaerobic Transformation in Soil	OECD 307	Refesol 01-A: $DT_{50\ soil,\ [FOMC],\ [20ºC]}$ = 11.08 Refesol 02-A: $DT_{50\ soil,\ [FOMC],\ [20ºC]}$ = 12.58 Refesol 05-G: $DT_{50\ soil,\ [SFO],\ [20ºC]}$ = 82.87 Refesol 06-A: $DT_{50\ soil,\ [FOMC],\ [20ºC]}$ = 8.239 **geometric mean (20°C): 17.6** **$DT_{50\ soil}$ = 17.6 d** Mineralisation: 2.9- 21.1 % (volatile traps). Bound residues (after acid and base extraction): 6.7-37.7 % Relevant metabolites: 2, 3, 4 for all soils, 6 for soil 01-A and 7 for soil 06-A.

Study type	Test protocol	Result	Remarks*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50 (growth) = 224 µg/l	
Daphnia sp. immobilisation	OECD 202	EC50 = 48100 µg/l	
Fish, acute toxicity/*species*	OECD 203	LC50 = 31430 µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	≤ 25% of control at 5.02 mg/kg.	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50 (growth) = 13200 µg/kg NOEC (growth) = 1200 µg/kg EC10 (growth) = 1150 µg/kg	6 species: most sensitive *Allium cepa* – Onion.
Earthworm/ *Eisenia foetida* reproduction	OECD 222	NOEC (mortality) > 621000 µg/kg NOEC (weight) > 621000 µg/kg	

		NOEC (reproduction) > 621000 µg/kg	

* Results are expressed in terms of active substante (i.e. Valnemulin HCl)

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Weaner pig

Compartment	PNEC	PEC	RQ
surface water (Cianobacteria, EC10)	6.4	3.22	0.50
groundwater		< 0.1 µg/l	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil (terrestrial plants, NOEC)	104	2189.6 ug/kg	**21.04**

Rabbit

Compartment	PNEC	PEC	RQ
surface water	2.24 ug/L	0.67	0.33
groundwater		< 0.1 µg/l	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil (terrestrial plants)	104	454.36	**4.4**

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water, groundwater, compartments indicating that the product will not pose a risk to those compartments when used as recommended. Regarding soil, RQs below 1 were obtained for soil microorganisms and earthworms.

The results of the assessment for terrestrial plants indicate a risk for the environment (RQ above 1) and therefore, the following risk mitigation measures are required for this VMP: Valnemulin is toxic for terrestrial plants.

The following information on environmental properties needs to be included in the product literature: Valnemulin is persistent in soil.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	The Log Pow of the active substance is <4.	not B

Persistence	$DT_{50,\ compartment,\ 12\ °C}$	176,07	P
Toxicity	EC_{10}	0.064 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

3.B. Residues documentation

Residue tests

No residue depletion studies were conducted because this is a generic application according to Article 18, and bioequivalence with the reference product has been demonstrated.

Maximum Residue Limits

Valnemulin is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	**Marker residue**	**Animal Species**	**MRL**	**Target tissues**	**Other provision**	**Therapeutic Classification**
Valnemulin	Valnemulin	Porcine, rabbit	50 µg/kg 500 µg/kg 100 µg/kg	Muscle Liver Kidney	No entry	Anti-infectious agents/Antibiotics

Withdrawal Periods

The same withdrawal periods than the reference product are proposed:

Pigs:
Meat and offal: 1 day.

Rabbits:
Meat and offal: Zero days.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

4.A. Pre-Clinical Studies

No pre-clinical studies were performed.

4.B. Clinical trials

No clinical trials were performed.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

None