DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0340/001/DC
Name, strength and pharmaceutical form	BIOTILINA 100 mg/g premix for medicated feed for pigs and rabbits
Applicant	VETPHARMA ANIMAL HEALTH, S.L Les Corts, 23 08028 Barcelona SPAIN
Active substance(s)	Valnemulin Hydrochloride
ATC Vetcode	QJ01XQ02
Target species	Pigs and 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.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	01/04/2020
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	DK, EL, FR, HU, IT, PT, RO

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product 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 product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 100 mg/g of valnemulin as active substance and paraffin, light liquid as a lubricant, silicon dioxide E 551, as a flowability power agent and almond shell as diluent.

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

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

B. Method of Preparation of the Product

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

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Valnemulin Hydrochloride, an established substance described in the European Pharmacopoeia. 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.

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products (pharmaceuticals)

NA

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 product.

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.

The demonstration of the batch to batch consistency is based on the results of three batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F. Stability

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 product throughout its shelf life when stored under the approved conditions.

The claim of a 6 months stability after first opening the immediate packaging is satisfactorily demonstrate.

G. Other Information

Appropriate data have been provided regarding the medicated feeding-stuff to demonstrate that a homogeneous stable mixing of the active substance is likely to be achieved in the final feed.

Stability data after incorporation into meal pig feed, pelleted pig feed and into pelleted rabbit feed have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, results of tests are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the user warnings proposed by the applicant address the identified risks of the product and have been updated in order to reflect the conclusions of the URA.

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

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 weaner pig and PECsoil initial = 454.36 µg/kg for rabbits) 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 constants in water pKa	OECD 112	pKa = 7.557 ± 0.035 pKb = 6.443 ± 0.035	
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	Log Pow = 1.924 (20ºC)	
Molecular mass	The Merck Index	564.83 g/mol	

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
UV-Vis Absorption spectrum	OECD 101	Acidic = 215.5-288.5 nm Neutral = 215.5-288.5	
Melting point	OECD 102	90.1-155 ºC	
Vapour pressure	OECD 104	Vapour pressure at 20 °C: 1.31 * 10^{-05} Pa Vapour pressure at 25 °C: 2.04 * 10^{-05} Pa	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	IME 01-A Koc = 1219.4 (Clay: 6.1%; Corg: 0.80%; pH: 4.72) IME 02-A: Koc = 3271.0 (Clay: 15.7%; Corg: 0.92%; pH: 6.19) IME 03-G: Koc = 1712.8 (Clay: 22%; Corg: 2.46%; pH: 5.71) IME 05-G: Koc = 7029.1 (Clay: 19.1%; Corg: 1.89%; pH: 4.44) IME 06-A: Koc = 3832.3 (Clay: 47.2%; Corg: 2.60%; pH: 7.27) Geometric mean **Koc = 2837.7 ml/g**	List all values with pH, Corg, soil texture including clay content
Aerobic and Anaerobic Transformation in Soil	OECD 307	Refesol 01-A: DT50 soil, [FOMC], [20ºC] = 11.08 Refesol 02-A: DT50 soil, [FOMC], [20ºC] = 12.58 Refesol 05-G: DT50 soil, [SFO], [20ºC] = 82.87 Refesol 06-A: DT50 soil, [FOMC], [20ºC] = 8.239 **DT50 soil geometric mean (20°C): 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	

Environmental fate			
		all soils, 6 for soil 01-A and 7 for soil 06-A.	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50 (growth, measured concentration)	224	µg a.s/l	*Static test.*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC10 NOEC	64 13.7	µg a.s/l	*Tier B*
Daphnia sp. immobilisation	OECD 202	EC50 (measured concentration)	48100	µg a.s/l	Static test.
Fish, acute toxicity/*species*	OECD 203	LC50 (measured concentration)	31430	µg a.s/l	Static test.
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	≤ 25% of control at 5.02 mg/kg		Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50 (worst-case; growth)	11930	µg Valnemulin base/kg	6 species: Avena sativa (oat), Allium cepa (onion), Brassica rapa (turnip), Solanum lycopersicum (tomato), Helianthus annuus (sun flower), Phaseolus aureus (mung bean)
Terrestrial Plants, growth test	OECD 208	EC10 (growth) NOEC (growth)	1040 1080	µg Valnemulin base/kg	*Tier B* 6 species: Avena sativa (oat), Allium cepa (onion), Brassica rapa (turnip), Solanum lycopersicum (tomato), Helianthus annuus (sun

					flower), Phaseolus aureus (mung bean)
Terrestrial Plants, growth test	OECD 208	EC50 (growth) NOEC (growth)	18270 2050	µg a.s/kg	*Tier C* 6 species: *Avena sativa (oat), Allium cepa (onion), Brassica rapa (turnip), Helianthus annuus (sunflower), Lactuca sativa (lettuce), Solanum lycopersicum (tomato), Phaseolus aureus (mung bean), Zea mays (corn)*
Earthworm/*Enchytraeidae* reproduction	OECD 220/222	NOEC Mortality Weight Reproduction	 621000 621000 621000	µg a.s/kg	

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:

Compartment	**PNEC**	**PEC**	**RQ**
surface water (Tier A; Cianobacteria; Weaner pig)	2.24	3.22 µg/L	**1.43**
surface water (Tier B; Cianobacteria; Weaner pig)	6.4	3.22 µg/L	0.5
surface water (Tier A; Cianobacteria;	2.24	0.67 µg/L	0.33

Rabbit)			
groundwater	NA	< 0.1 µg/L	NA
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil (Tier A; Terrestrial Plants; Weaner pig)	119.3	2189.6 µg/Kg	**18.35**
Soil (Tier B; Terrestrial Plants; Weaner pig)	102	2189.6 µg/Kg	**20.27**
Soil (Tier C; Terrestrial Plants; Weaner pig)	182.7 (EC50) 205 (NOEC)	2189.6 µg/Kg	**11.98** **10.68**
Soil (Tier A; Terrestrial Plants; Rabbit)	119.3	454.36 µg/Kg	**3.80**
Soil (Tier B; Terrestrial Plants; Rabbit)	102	454.36 µg/Kg	**20.27**
Soil (Tier C; Terrestrial Plants; Rabbit)	182.7 (EC50) 205 (NOEC)	454.36 µg/Kg	**2.48** **2.21**

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

The results of the assessment for the soil compartments indicate a risk for terrestrial plants. The following information on environmental properties needs to be included in the product literature *Risk is identified for terrestrial plants*.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Log Pow < 4	not B
Persistence	$DT_{50,\ soil,\ 12\ °C}$	176.07	P
Toxicity	$E(L)C_{50}$	>0.1 µg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this application is in accordance with Article 13 (1) – Generic application of Directive 2001/82/CE and bioequivalence with a reference product has been demonstrated.

MRLs

The active substance VALNEMULIN is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010.

MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Valnemulin	Valnemulin	Porcine Rabbit	50 µg/kg 500 µg/kg 100 µg/kg	Muscle Liver Kidney	

The excipients:

	Included in Table 1 of Commission Regulation (EU) No 37/2010
Liquid Paraffin	Yes. As no MRL required for all food producing species.
Colloidal anhydrous silica	No. Included as feed additive according to EU Commission Regulation 2011/1130/EU as E-551
Almond shell	No. Included as Substances considered as not falling within the scope of Regulation (EC) No. 470/2009

Withdrawal Periods

The proposed meat and offal withdrawal periods for the BIOTILINA are the same as for the reference product:
Pigs:
Meat and offal: 1 day.

Rabbits:
Meat and offal: Zero days.

This is considered to be acceptable and in line with the current bioequivalence and withdrawal period calculation guidelines.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC. As bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

As this was a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC, and Bioequivalence with a reference product was demonstrated, pre-clinical studies are not required.

IV.B Clinical Studies

As this was a generic application according to Article 13(1) of Directive 2001/82/EC, amended by Directive 2004/28/EC, and Bioequivalence with a reference product was demonstrated, clinical studies are not required.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product 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 product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None