Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

TYAWALT 450 mg/g
granules for use in drinking water for pigs, chickens and turkeys

Date: 17 August 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0264/001/DC
Name, strength and pharmaceutical form	Tyawalt 450 mg/g granules for use in drinking water for pigs, chickens and turkeys
Applicant	HCS bvba H. Kennisstraat 53 2650 Edegem Belgium
Active substance(s)	Tiamulin hydrogen fumarate
ATC Vetcode	QJ01XQ01
Target species	Pigs, chickens and turkeys
Indication for use	Pigs Treatment of Swine Dysentery caused by Brachyspira hyodysenteriae susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used. Treatment of Porcine Colonic Spirochaetosis (colitis) caused by Brachyspira pilosicoli susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used. Treatment of Porcine Proliferative Enteropathy (ileitis) caused by Lawsonia intracellularis susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used. Treatment and metaphylaxis of Enzootic Pneumonia caused by Mycoplasma hyopneumoniae, including infections complicated by Pasteurella multocida susceptible to tiamulin. The presence of the disease in the herd must be established before

	the product is used. Treatment of Pleuropneumonia caused by Actinobacillus pleuropneumoniae susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used. Chickens Treatment and metaphylaxis of Chronic Respiratory Disease caused by Mycoplasma gallisepticum and Airsacculitis and Infectious Synovitis caused by Mycoplasma synoviae susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used. Turkeys Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by Mycoplasma gallisepticum, Mycoplasma synoviae and Mycoplasma meleagridis susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	20 December 2017
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	BE, DK, ES, FR, NL, PL, PT and UK

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 overall risk/benefit analysis is in favour of granting a marketing authorisation.
The safety and efficacy aspects of this product are identical to Denagard 45% Granulat (Novartis Tiergesundheit GmbH). The initial application for Denagard 45% Granulat was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 450 mg tiamulin hydrogen fumarate per gram and the excipient lactose monohydrate.

The container/closure system consists of low-density polyethylene-aluminium-polyethylene terephtalate laminated bags.

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 at a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is tiamulin hydrogen fumarate, 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 and/or certificates of suitability issued by the EDQM 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

Not applicable.

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 have been provided demonstrating compliance with the specification.

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.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated, safety studies are not required.

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

III.A Safety Testing

Pharmacological Studies

Regarding the pharmacodynamic documentation of this application, full reference was made to the reference product.

Toxicological Studies

The generic product contains the same active substance and the same excipients in the same concentrations as an approved reference veterinary medicinal product and is intended to be used by the same route of administration (i.e. in drinking water) in the same target species and in the same dose regimen as the reference product.

User Safety

The product is safe for the user, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

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 is greater than 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	3250 - 9200mg/L at pH 5.4 - 8.2	
Dissociation constants in water pKa	OECD 112	pKa = 7.44	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	1.2 – 4.4 at pH 5.5 – 8.5	

Environmental fate			
Soil	OECD	Koc = 536 – 7312 kg/L	

Environmental fate			
Adsorption/Desorption	106		
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 20\ °C.}$ = 10.2 – 55.5 d $DT_{50,\ 20\ °C.\ geo.\ mean}$ = 15.6 d $DT_{50,\ 12\ °C,\ worst\ case}$= 118.5 d Transformation products >10%: *Unknown signals 1, 2, 3 and 6* $DT_{50,\ 12°C,\ unknown\ signal\ 3}$= 208.1 d % non-extractable residues (NER): 5.4 – 34.05 % at D 120	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Cyanobacteria, growth inhibition test/ *Anabaena flos aqua*	OECD 201	EC50	148	µg/l	
Algae and or cyanobacteria, growth inhibition test/ *Anabaena flos aqua*	OECD 201	NOEC ErC10	3.6 15	µg/l	*Tier B*
Daphnia sp. immobilisation	OECD 202	EC50	46100	µg/l	
Fish, acute toxicity/ *Oncorhynchus mykiss*	OECD 203	LC50	18400	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	23 % effect	27 000	µg/kg	No significant deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	18 400	µg/kg	Tier A : 4 species
Terrestrial Plants, growth test	OECD 208	NOEC	4600	µg/kg	*Tier B:* 6 species

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Terrestrial Plants, growth test; in soil spiked with broiler chicken manure for 21 days	OECD 208; modified	NOEC	3600	µg/kg	*Tier B:* 6 species:
Earthworm/*Enchytraeidae* reproduction	OECD 222	NOEC	≥ 1000	µg/kg	
Bioaccumulation in fish/*Brachydanio rerio*	OECD 305 Type: Flow-through	BCF_{SS} BCF_k	16.7 20.9	l/kg l/kg	

*add information on analytical verification of test substance (nominal (n) or measured (m)), on exposure (e. g. semi-static, flow-through, sediment spiked, etc.), on test substance (salt, base), and on test medium (e. g. Corg content)

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	1.5 µg/l	3.92 µg/l	2.6
groundwater	No exposure		
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	360 µg/kg	1109 µg/kg	3

The results of the assessment for the surface water and soil compartments indicate a risk for the environment. Risk mitigation measures are not feasible in case of

spreading manure on arable or grass land. Further information and a revised risk assessment will be provided by the first renewal.

The following information on environmental properties have been included in the product literature:

A transformation product of tiamulin is very persistent in soil. Tiamulin may be toxic to plants and algae.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	20.9 l/kg	not B
Persistence	$DT_{50,\ soil,\ 12\ °C}$	TP 3; 208 d	vP
Toxicity	NOEC	0.0036 mg/l (Algae)	T
PBT-statement :	The compound is not considered as PBT nor vPvB.		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted as this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated. The reference product is authorised with the same withdrawal periods as claimed for Tyawalt 450 mg/g.

MRLs

Tiamulin is listed in Table 1 of Commission Regulation (EU) No 37/2010 with the following MRLs:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin	Porcine	100 µg/kg 500 µg/kg	Muscle Liver	
		Chicken	100 µg/kg 100 µg/kg 1000 µg/kg	Muscle Skin + fat Liver	
		Turkey	100 µg/kg 100 µg/kg 300 µg/kg	Muscle Skin + fat Liver	
	Tiamulin	Chicken	1000 µg/kg	Eggs	

Withdrawal Periods

The following withdrawal periods were accepted:

Pigs:	Meat and offal:	7 days
Chicken:	Meat and offal:	3 days
	Eggs:	Zero days
Turkeys:	Meat and offal.	4 days

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with the 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

Pharmacology

Regarding the pharmacodynamic documentation of this application, full reference was made by the applicant to the reference product.

Tolerance in the Target Species of Animals

Regarding the target animal tolerance documentation of this application, full reference was made by the applicant to the reference product.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Regarding the resistance documentation of this application, reference was made by the applicant to the reference product.

Additional bibliography provided suggests that resistance of most target pathogens remains favourable except for B. hyodysenteriae where the MIC distribution for tiamulin is bimodal, suggesting reduced susceptibility of some strains to tiamulin.

Adequate warnings and precautions including responsible use warnings appear on the product literature.

IV.B Clinical Studies

Regarding the clinical documentation, full reference was made by the applicant to the reference product.

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 Heads of Veterinary Medicinal 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>