College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

T.S.-sol 20/100, solution for use in drinking water for pigs and chickens

Create: August 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0213/001/DC
Name, strength and pharmaceutical form	T.S.-sol 20/100, 20 mg trimethoprim and 100 mg sulfamethoxazole/ml, solution for use in drinking water for pigs and chickens
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Trimethoprim and sulfamethoxazole
ATC Vetcode	QJ01EW11
Target species	Pigs (fattening pigs) and chickens (broilers)
Indication for use	Fattening pigs: Treatment and metaphylaxis of: - Post weaning diarrhoea caused by ß-haemolytic K-88positive, K99- positive or 987P *Escherichia coli* strains susceptible to trimethoprim-sulfamethoxazole. - Secondary bacterial infections caused by *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Streptococcus spp.* and *Haemophilus parasuis* susceptible to trimethoprim-sulfamethoxazole. Broilers: Treatment and metaphylaxis of: - Colibacillosis caused by *Escherichia coli* susceptible to trimethoprim-sulfamethoxazole. - Coryza caused by *Avibacterium paragallinarum* susceptible to trimethoprim-sulfamethoxazole. The presence of the disease in the group/flock must be established before the product is used.

Product name: T.S.-sol 20/100, 20 mg trimethoprim and 100 mg sulfamethoxazole/ml, solution for use in drinking water for pigs and chickens	Application number: NL/V/0213/001/DC
Applicant: Dopharma Research B.V.	DCP
	Publicly available assessment report

MODULE 2

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

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	Publicly available assessment report

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	28-06-2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Belgium, Germany, Denmark, Greece, Spain, France, Croatia, Hungary, Italy, Poland, Romania, United Kingdom

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 and the consumer of foodstuffs from treated animalst, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
A risk for the soil compartment was identified in the environmental risk assessment.
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 per ml 20 mg trimethoprim and 100 mg sulfamethazole and the excipients N-methylpyrrolidone, propylene glycol, sodium hydroxide and purified water.

The container/closure system consists of a white 1 L HDPE bottle with LDPE screw cap, and a white 5 L HDPE jerrycan with a HDPE screw cap

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product 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.

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

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

C. Control of Starting Materials

The active substance is Trimethoprim and sulfamethoxazole, 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.

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

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

F. Stability

Stability data on the active substances 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 a reference product has been demonstrated, results of toxicological, pharmacological and residue tests are not required.

The aspects of this product are identical to the reference product.

Warning statements and precautions as listed in the product literature are based on those of the reference product and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to the animals, users, consumers and the environment.

III.A Safety Testing

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological, pharmacological and residue tests are not required.

User Safety

Being a generic procedure the applicant refers to the reference product for information on this section.
Additionally the applicant has provided a user safety assessment. Combined with increased knowledge and the current state of science, warning statements and precautions have been added to the product literature, ensuring safety to users of the product.

Environmental Risk Assessment

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

Phase I:

A Phase II ERA was required for both ingredients as the Phase I assessment showed that the initial predicted environmental concentration in soil ($PEC_{soil\ initial}$ = 1521 µg/kg for Sulfamethoxazole and 304 µg/kg for Trimethoprim) is greater/equal to 100 µg/kg and no mitigations exist that alter the PEC_{soil}.

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 of sulfamethoxazole			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	194 mg/L	17 -20 °C
Dissociation constants in water pKa	OECD 112	pKa = 5.909	20°C
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	logK_{ow} 0.9 at pH 4 and 20 ± 1°C = logK_{ow} -0.2 at pH 7 and 20 ± 1°C logK_{ow} ≤ 1.6 at pH 9 and 20 ± 1°C	

Physical-chemical properties of trimethoprim			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	400 mg/L	25°C
Dissociation constants in water pKa	OECD 112	pKa = 6.6	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107 or 117 or 123	logK_{ow} 0.952 ± 0.0033 at pH 3.5… and 25°C	pH 3.5
Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc value for sulfamethoxazole = 375.8 dm^3 kg^{-1} Koc value for trimethoprim = 4252.6 dm^3 kg^{-1}	Average of five soils Average of seven soils

Effect studies was performed with both trimethoprim and sulfamethoxazole in the product'[s therapeutic

ration (1:5)					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
cyanobacteria, growth inhibition test/*species Anabaena flos-aquae*	OECD 201	EC50	>100	>100 mg/L	
Daphnia sp. immobilisation	OECD 202	EC50	>45.5	>45.5 mg/L	
Fish, acute toxicity/*species* *Oncorhynchus mykiss*	OECD 203	LC50	100	>100 mg/L	
Terrestrial Plants, growth test	OECD 208	EC10 NOEC EC50	0.316 0.333 0.739	Mg/kg	*Tier B* *Brassica napus*
		EC10 NOEC EC50	3.28 3.0 25.9	Mg/kg	*Glycine max*
		EC10 NOEC EC50	1.74 3.0 5.48	Mg/kg	*Beta vulgaris*
		EC10 NOEC EC50	9.94 3.0 31.3	Mg/kg	*Helianthus annuus*
		EC10 NOEC EC50	3.02 3.0 16.3	Mg/kg	*Lycopersicon esculentum*
		EC10 NOEC EC50	5.47 3.0 53.0	Mg/kg	*Cucumis sativus*
		EC10 NOEC EC50	0.203 0.333 3.63	Mg/kg	*Fagopyrum esculentum*
		EC10	8.59	Mg/kg	*Avena sativa*

		NOEC EC50	9.0 20.1		
		EC10 NOEC EC50	0.656 1.0 2.03	Mg/kg	*Lolium perenne*
		EC10 NOEC EC50	5.32 9.0 48.1	mg/kg	*Allium cepa*
Earthworm reproduction	OECD 220/	or NOEC	≥23.42	Mg/kg	Eisenia fetida

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			
- Weaner pig	Algea: > 1000 µg/ l Crustaceans: > 45.5 µg/ L Fish: >100 µg/ L	19.1 µg/ L	Algea: 0.02 µg/ l Crustaceans: 0.42 µg/ L Fish: 0.19 µg/ L
- Fattening pig	Algea: > 1000 µg/ l Crustaceans: > 45.5 µg/ L Fish: >100 µg/ L	13.0 µg/	Algea: 0.01 Crustaceans: 0.29 µg/ L Fish: 0.13 µg/ L
- Sow+ litter	Algea: > 1000 µg/ L Crustaceans: > 45.5 µg/ L Fish: >100 µg/ L	4.6 µg/ L	Algea: 0.005 µg/ l Crustaceans: 0.10 µg/ L Fish: 0.05 µg/ L
- Broiler	Algea: > 1000 µg/ l Crustaceans: > 45.5	12.5 µg/ L	Algea: 0.013 µg/ L

	µg/ l Fish: >100 µg/ L		Crustaceans: 0.28 µg/ L Fish: 0.13 µg/ L
groundwater	No specific PNECs are available. The PNECs for surface water are taken as representative.		
- Weaner pig		57.3 µg/ L	
- Fattening pig		38.9 µg/ L	
- Sow+litter		13.8 µg/ L	
- Broiler		37.6 µg/ L	
soil microorganisms: Nitrogen transformation test concentration of 1.2 mg/kg and 11.7 mg/kg PEC_{soil}	<No effect on the nitrogen formation of more than>25% difference in N transformation	NA	NA
soil			
- Weaner pig	Micro-organisms: Earthworms: ≥2342 µg/ kg Plants: 7.39 µg/ kg	1825 µg/ kg	Micro-organisms:n.c Earthworms: ≥0.78 µg/ kg Plants:247 µg/ kg
- Fattening pig	Micro-organisms: n.c Soil earthworms: ≥2342 µg/ kg Plants: 7.39 µg/ kg	1238 µg/ kg	Micro-organisms: n.c Earthworms: ≥0.53 µg/ kg Plants: 167 µg/ kg
- Sow+litter	Micro-organisms: Soil earthworms: ≥2342 µg/ kg Plants: 7.39 µg/ kg	439 µg/ kg	Micro-organisms: n.c Earthworms: ≥0.19 µg/ kg Plants:59 µg/ kg
- Broiler	Micro-organisms:	1197 µg/	Micro-organisms:

	Soil earthworms: ≥2342 µg/ kg Plants: 7.39 µg/ kg	kg	n.c Earthworms: ≥0.51 µg/ kg Plants:162 µg/ kg

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water compartment and for the groundwater compartment the calculated PEC is lower than 0.1 µg/L. This indicates that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the soil compartment indicate that a risk for the environment is indicated and this should be considered in the risk benefit analysis. No acceptable risk mitigation measures were suggested.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF		not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

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

Withdrawal Periods

Based on the above the following withdrawal periods are justified:

Pig: Meat and offal: 8 days.

Chicken: Meat and offal: 5 days.

Not authorised for use in birds producing eggs for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and 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.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

Although a risk for the soil compartment was identified it was concluded that when the product is used in accordance with the agreed Summary of Product Characteristics, the risk benefit profile for the product is favourable..

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 Vetrinary Medicines 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.

18 November 2020	B.II.1.a.2 Updated certificate from an already approved manufacturer (NL/V/0213/001/IA/002)
5 July 2018	B.III.1.a.2 Updated certificate from an already approved manufacturer (NL/V/0213/001/IA/001)