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AGENCE NATIONALE DE SÉCURITÉ SANITAIRE de l'alimentation, de l'environnement et du travail
FRENCH AGENCY FOR FOOD, ENVIRONMENTAL AND OCCUPATIONAL HEALTH AND SAFETY
14 rue Claude Bourgelat – PA de la Grande Marche – Javené - CS 70611 – F-35306 FOUGERES Cedex

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Hydrotrim 500 mg/g + 100 mg/g powder for use in drinking water/milk for cattle, sheep, pigs and chickens

14 September 2023

PRODUCT SUMMARY

EU procedure number	FR/V/0457/001/DC
Name, strength and pharmaceutical form	Hydrotrim 500 mg/g + 100 mg/g powder for use in drinking water/milk for cattle, sheep, pigs and chickens
Applicant	HUVEPHARMA / UITBREIDINGSTRAAT 80 – 2600 ANTWERPEN – BELGIUM
Active substance(s)	Sulfadiazine (as sulfadiazine sodium), Trimethoprim
ATC vetcode	QJ01EW10
Target species	Cattle (pre-ruminant calves), sheep (pre-ruminant lambs), pigs and chickens.
Indication for use	<u>Cattle (pre-ruminant calves) and sheep (pre-ruminant lambs)</u> Treatment and metaphylaxis of respiratory infections caused by *Mannheimia haemolytica* or *Pasteurella multocida* and infections caused by *Escherichia coli*. The presence of the disease in the group must be established before the veterinary medicinal product is used. <u>Pigs</u> Treatment and metaphylaxis of respiratory infections caused by *Actinobacillus pleuropneumoniae* or *Pasteurella multocida* and infections caused by *Streptococcus suis* or *Escherichia coli*. The presence of the disease in the group must be established before the veterinary medicinal product is used. <u>Chickens</u> Treatment and metaphylaxis of colibacillosis caused by *Escherichia coli*. The presence of the disease in the flock must be established before the veterinary medicinal product is used.

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HUVEPHARMA	DCP
Publicly available assessment report	

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 (EC) 2019/6.
Reference product (RP)	ADJUSOL TMP SULFA LIQUIDE 16,65 MG/ML + 83,35 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON/LAIT (10328)
Marketing authorisation holder	Virbac France
MS where the RP is or has been authorised	France
Marketing authorisation number EU procedure number	MA number: FR/V/7769292 8/1988
Date of authorisation	22/06/1988
Date of completion of the original decentralised procedure	26/07/2023
Concerned Member States for original procedure	AT - BE - BG - CY - CZ - DE - DK - EE - EL - ES - HR - HU - IE - IS - IT - LT - LU - LV - MT - NL - PL - PT - RO - SI - SK - UK (NI)

*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

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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

A. Product description

The VMP is a powder for use in drinking water/milk, which contains 100 mg/g trimethoprim and 500 mg/g sulfadiazine and the excipients polysorbate 80 and maltodextrin.

The container/closure system is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative is justified.

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

B. Description of the manufacturing method

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

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

C. Production and control of starting materials

One active substance is trimethoprim, an established substance described in the European Pharmacopeia. The second active substance is sulfadiazine, used as a sodium salt, an established substance, not described in the European Pharmacopeia. Both active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substances specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Scientific data has been provided for sulfadiazine (as sodium salt), and certificate of suitability issued by the EDQM has been provided for trimethoprim.

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

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

The control tests and specification have been justified and are considered appropriate to adequately control the quality of the isolated intermediates. Containers are suitable for storage and transport of these intermediates.

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 sites have been provided demonstrating compliance with the specification.

F. Stability tests

Stability data on both active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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.

An in-use shelf-life and a shelf-life after dilution in drinking water or milk as detailed on the SPC have been supported by appropriate data.

G. Other information

Not Applicable.

3. SAFETY DOCUMENTATION (safety and residues tests)

A. Safety tests

Pharmacological studies

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with the reference veterinary medicinal product ADJUSOL TMP SULFA LIQUIDE 16,65 MG/ML + 83,35 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON/LAIT has been demonstrated, results of pharmacological studies 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.

Development of resistance and related risk in humans

The applicant has provided a satisfactory antimicrobial resistance risk review for HYDROTRIM in line with the new requirement of the Regulation (EU) 2019/6, Article 8 (2), and Annex II.3A.4.3.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the risk for the user of the product is similar to the one of 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 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/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.

<u>TRIMETHOPRIM</u>

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	Merck index value	400 mg/L	
Dissociation constants in water pKa	Merck index value	pKa = 6.6	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	logK_{ow} = 0.952	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Kfoc = 1133 (pH 4.32), 1613(pH 5.87), 8117(pH 7.26), 5179 (pH 4.37), 1905 (pH 3.60), 816 (pH 3.24), 11005 (pH 7.27) in loam (2.3), loam	

Environmental fate			
		(2.7), clay (2.7), clay loam (2.9), loamy sand (1.7), loamy sand (9.4) and clay (2) soils (OC%) respectively	
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 20°C,\ SFO}$ = 53.3, 57.4, 60.7, 42.06 and 15.7 days in loam (2.3), loamy sand (0.8), sandy loam (1.4), clay (2.7) and soils (OC%) respectively (%NER 29.2, 28.3 and 21.9) $DT_{50,\ 12°C\ worst\ case.}$ = 129.9 days	

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	69.49	mg/l	The coefficients of variation for section-by-section growth rates mean are too high (>10% for day 0-1 and day 1-2 respectively). The results of this study are assessed as acceptable with restrictions.
Daphnia sp. immobilisation	OECD 202	EC50	22.3	mg/l	
Fish, acute toxicity/*species*	OECD 203	LC50	>50	mg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25% difference in N transformation	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	133.6 (*R. sativus*)	mg/kg	*Triticum aestivum, Alium cepa , Glycine max, Solanum lycopersicum, Cucumis sativus, Raphanus sativus*
Enchytraeidae reproduction	OECD 220	NOEC	>100	mg/kg dw	

*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	22.3 µg/L	1.58 µg/L	0.07
groundwater		<0.1 µg/L (Focus)	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	1336 µg/kg	310 µg/kg	0.23

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

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	log Kow <4 (0.9)	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	> 120 (129.9)	P
Toxicity	NOEC or CMR	Not required	T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as P		

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

SULFADIAZINE

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	Merck index value	130 mg/L at pH 5.5 2000 mg/L at pH 7.5	
Dissociation constants in water pKa	Merck index value	pKa1 = 1.57 pKa2 = 6.50	
Melting point	Merck index value	252-256	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	logK_{ow} = 0.027	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Geometric mean Kfoc = 95.8	Peer-reviewed literature covering a large range of soil textures (clay content 4.0 to 68.4 %), pH (3.7

Environmental fate			
			to 8.5) and organic carbon contents (0.5 to 21.3 %)
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 20°C,\ SFO}$ = 1.03, 1.04, 6.19, 5.43 and 4.58 days in loam (2.3), loamy sand (0.8), sandy loam (1.4), clay (2.7) and soils (OC%) respectively (%NER 29.2, 28.3 and 21.9) $DT_{50,\ 12°C\ worst\ case.}$ < 120 days	

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	28.46	mg/l	
Daphnia sp. immobilisation	OECD 202	EC50	188	mg/l	Proprietary study and 3 reliable published studies
Fish, acute toxicity/*species*	OECD 203	LC50	> 137.6	mg/l	Limit test
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25% difference in N transformation	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	13 (*B. rapa*)	mg/kg	*Avena sativa , Zea mays, Cucumis sativa, Lycopersicon esculentum, Brassica rapa, Vigna angularis*
Terrestrial Plants, growth test	OECD 208	NOEC	5 (*B. rapa*)	mg/kg	Tier B 6 species: (cf above list)
Enchytraeidae reproduction	OECD 220	NOEC	> 100	mg/kg dw	

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	137	91 µg/l (Step 2)	0.66
groundwater		<0.1 µg/L (Focus)	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	130	1.55 mg/kg	11.94

The risk characterisation resulted in risk quotient below 1 for the surface water, compartment indicating that the product will not pose a risk to this compartment when used as recommended.

The results of the assessment for the soil compartment indicate that a risk for the environment is indicated in phase 2 tier A.

Tier B risk characterisation:

Compartment	PNEC	PEC	RQ
soil	500 µg/kg	1.55 mg/kg	3.1

The results of the assessment for the soil compartment indicate that a risk for the environment is indicated in phase 2 tier B.

SSD assessment

Two additional dicotyledenoa species were tested, *Helianthus annuus* and *Beta vulgaris*

Overall, data are available on the chronic effect of sulfadiazine to eight plant species allowing the use of SSD approach:

Compartment	PNEC	PEC	RQ
soil	1750 µg/kg (LL HC5)	1.55 mg/kg	0.89

The risk characterisation resulted in risk quotient below 1 for the soil, compartment indicating that the product will not pose a risk to this compartment when used as recommended.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	log Kow <4 (0.9)	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	< 120	not P
Toxicity	NOEC or CMR	Not required	T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

Combined risks

Compartment	Taxa	TMP RQ	Sulfa RQ	Combined RQ
Terrestrial	Terrestrial invertebrates	0.0031[a]	0.16[a]	0.16
	Plants	0.23[a]	0.89[b]	1.12[c]
Freshwater	Algae	0.0023[a]	0.32[a]	0.32
	Invertebrates	0.071[a]	0.48[a]	0.55
	Fish	0.032[a]	0.66[a]	0.69

[a] - risk quotient established individually for the compound during Phase II Tier A
[b] - risk quotient established for the compound during the Phase II higher tier assessment
[c] - risk quotient less than 1 when a Phase II Tier B risk quotient for trimethoprim is considered

B. Residues documentation

Residue tests

No residue depletion studies were conducted.

Maximum Residue Limits

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

SULFONAMIDES (all substances belonging to the sulfonamide group)						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
Parent drug	All food producing species	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg	Muscle Fat Liver Kidney	The combined total residues of all substances within the sulfonamide group should not exceed 100 µg/kg. For fin fish the muscle MRL relates to « muscle and skin in natural proportions ». MRLs for fat, liver and kidney do not apply for fish. Not for use in animals from which eggs are produced for human consumption.	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009
	Bovine, ovine, caprine	100 µg/kg	Milk			

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

TRIMETHOPRIM						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
trimethoprim	*Equidae*	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg	Muscle Fat Liver Kidneys	For fin fish the muscle MRL relates to « muscle and skin in natural proportions ». MRLs for fat, liver and kidney do not apply for fin fish. For porcine and poultry species, the fat MRL relates to "skin and fat in natural proportions". Not for use in animals from which eggs are produced for human consumption.	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009
	All other food producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Fat Liver Kidneys Milk			

Withdrawal Periods

It is a generic application submitted according to Article 18 of Regulation (EC) 2019/6. The withdrawal periods are the same as those for the reference VMP, as follows:

Calves

Meat and offal: 12 days.

Lambs

Meat and offal: 12 days.

Pigs

Meat and offal: 12 days.

Chickens

Meat and offal: 12 days.

Not for use in birds producing or intended to produce eggs for human consumption.

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 and target animal safety studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP. The target animal safety profile of this VMP will be the same as that of the reference VMP, and therefore the text in sections 3.6 and 3.10 of the proposed SPC is in line with the text agreed for the reference VMP. Adequate warnings and precautions appear on the product literature regarding the development of resistance and related risk in animals.

In addition, the applicant conducted palatability studies in each target animal species in order to demonstrate the adequate uptake of medicated water, according to the Guideline EMA/CVMP/EWP/206024/2011. The palatability studies demonstrated that the water consumption was equivalent between the candidate and the reference products, according to the guideline requirements.

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.