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

FLORFENIS 300 mg/ml solution for injection for cattle, sheep and pigs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0377/001/DC
Name, strength and pharmaceutical form	FLORFENIS 300 mg/ml solution for injection for cattle, sheep and pigs
Applicant	LABORATORIOS SYVA, S.A.U. Avda. Parroco Pablo Diez, 49-57, 24010. San Andres Del Rabanedo. Leon - España -
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Bovine Ovine Porcine
Indication for use	Cattle: Treatment and Metaphylaxis of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol. The presence of the disease in the group must be established before metaphylactic treatment. Sheep**:** Treatment of ovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to florfenicol. Pigs: Treatment of acute outbreaks of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol.

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	D210: 16/12/20
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	CMSs: BE, DE, DK, EL, FR, HU, IE, IT, LT, NL, PL, PT, RO.

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 florfenicol (300 mg/ml) as active substance and a mixture of propylene glycol/N-methylpyrrolidone/macrogol 300 is used as vehicle. No other excipients are included in the formulation.

The medicinal product is packaged in type II colourless glass vials of 100 ml and 250 ml, sealed with type I bromobutyl rubber stoppers and aluminium caps.

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 florfenicol, an established active substance which is not described in a 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.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Confirmation is provided regarding compliance of the finished product with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

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 substance florfenicol 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 (2 years) when stored under the approved conditions.

Data submitted on in-use stability studies are considered sufficient to support an in-use shelf life of 28 days after broaching.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

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

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

Warnings and precautions as listed on the product literature are updated respect to those of the reference product and are adequate to ensure safety of the product to users, and the consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of toxicological studies are not required.

Excipients are commonly used in veterinary medicines for injection.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline for the assessment of the risks posed to the user as a result of the hazards identified for the excipient N-methyl-2-pyrrolidone which shows that the most likely routes of exposure may be accidental either via self-injection or via dermal and ocular route due to release of the product from the syringe.

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 = 107.59-pigs and 116.57-cattle, µg/kg) are greater/equal to 100 µg/kg and no mitigations exist that alter the PECsoil less than the cut off value.

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 (flask method)	1048.17 mg/L (at 20°C)	-
Dissociation constants in water pKa	OECD 112	pKa = 6.696 ± 0.085 7.304 ± 0.085	-
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 117	$logK_{ow}$ or $logD_{ow}$ at pH … Kow <0.3(revisar en el estudio el pH)	-

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Refesol 01-A (loamy sand, pH 5.55, 1.02% Corg, 6% clay)Koc = 29.4 Refesol 03-G (silt loam, pH 5.61 and adjusted to ~7.5 by addition of CaCO3, 4.03% Corg, 30% clay) Koc = 14.9 Refesol 06-A (silt clay loam, pH 6.86, 2.74% Corg, 44% clay) Koc = 21.9	List all values with pH, Corg, soil texture including clay content
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50, study temp., kinetics applied *DT50 florfenicol+u.i._2. (SFO kinetics, 20ºC* **DT50** / **DT90** Refesol 01 A: 22.4 / 74.5 REfesol 02 A: 7.2 / 23.8 Refesol 03 G: 4.8 / 15.9 Refesol 06 G: 12.9 / 42.9 Refesol 06 G (10ºC): 47.7 / 158.5 DT50 florfenicol+u.i_2= 10.0 d *DT50 florfenicol* **DT50** Refesol 01 A: 14	For each of the 4 soils. Information on soils used

Environmental fate			
		REfesol 02 A 5.2 Refesol 03 G 3.8 Refesol 06 G 8.8 Refesol 06 G (10ºC) 27.4 DT50 florfenicol = 7.024 d **Clay %** / **Corg%** / **pH** / **WHC (g/kg)** Refesol 01 A: 6 / 1.17 / 5.55 / 254 REfesol 02 A: 12 / 1.37 / 6.81 / 430 Refesol 03 G: 30 / 4.03 / 5.61(*) / 672 Refesol 06 G: 44 / 2.74 / 6.86 / 492 *) was adjusted to pH c.a. 7.5 $DT_{50,\ 12°C.\ geo.\ mean\ of\ 4x\ soils\ or\ worst\ case\ if\ <\ 4\ soils}$ = not calculated Transformation products >10%: u.i.1_TLCstart, u.i.2_TLC % non-extractable residues (NER): NER were further characterized in case >10% by extraction as: -Unsoluble humins, fulvic acids and humic acids. Humic acids are in all cases less than 10% Refesol 01 A: Unsoluble humins % 13.2% (d 120) / fulvic acids% 26.1% (d 60) / humic acids % <10 REfesol 02 A: 26.8% (d120) / 30.6% (d 14) / <10 Refesol 03 G: 18.2% (d 7) / 42.9% (d 21) / <10 Refesol 06 G: 20.7% (d 100) / 21% (d 28) / <10 Refesol 06 G (10ºC): 21.6% (d 60) / 20.9% (d 60) / <10	
Transformation in Manure (species)		$DT_{50,\ study\ temp.}$ = 0.2 d (20ºC) Transformation products >10% *<give name and structural formula>*	Temperature (at which study was conducted):

Environmental fate			
		% Transformation products: NIR1_TLC (polars) 49.7% at day 100, Total radioactivity florfenicol+NIR1+NER at day 59 (sterile soil): 1.5%+45.8%+14.1=61.4% % non-extractable residues (NER): % NER: 35% at day 59 (manure soil)	20ºC

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
cyanobacteria, growth inhibition test *Synechococcus leopoliensis*	OECD 201	EC50	EC50 (growth) = 210 EC10 (growth) = 140 NOEC (growth) = 46	µg/l	*Treatments 0.046 and 0.1 mg/L were not analysed (nominal concentrations below the LOQ).*
Daphnia sp. immobilisation	OECD 202	EC50	>100000	µg/l	nominal
Fish, acute toxicity/ *Danio rerio*	OECD 203	LC50	>100000	µg/l	nominal
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	No impact at 0.434 mg/kg soil (dw) Impact at 4.34 mg/kg soil (dw)		Trigger value: 25% deviation from the control
Soil micro-organisms: nitrogen transformation test (100 days)	OECD 216	% effect	42 d: No impact at 0.434 mg/kg soil (dw) No impact at 4.34 mg/kg soil (dw)		*Only if effect is shown after 28 days*
Terrestrial Plants, growth test	OECD 208	EC50, EC10 and NOEC	EC50= 130 *(B. vulgaris)* NOEC=20(*B. vulgaris)* EC10=10 (*B. vulgaris*)	µg/kg	*Tier B* 6 species: *H. bulgare, A. rapa, A.cepa, A.*

					sativa, T. aestivum, P. aureus, R. sativus, B. napus, B. vulgaris.
Terrestrial Plants, growth test *SSD*		LLHC5 (EC10)	3.32		*Tier C*
Earthworm reproduction	OECD 220/222	EC10 or NOEC	NOEC (weight) = 62500 NOEC (reproduction) = 62500	µg/kg (dw)	nominal

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 (cattle)	2.1 µg/L	2.84 µg/L (FOCUS SWASH, STEP 3 R3)	1.35
groundwater	1.4 µg/L (cyanobacteria)	1.4 µg/L (cattle) (FOCUS PEARL, Okehampton)	1
	MTCdw=30 µg/L (drinking water)		0.05
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	No risk
soil	3.32 µg/kg	116.57 µg/kg (cattle)	35.11

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

The results of the assessment for the surface water, groundwater (ecosystem) and soil compartments points that a risk for the environment is indicated. Benefit/Risk assessment was included in the evaluation resulting in a positive balance.

The following information on environmental properties needs to be included in the product literature: warning for toxicity to terrestrial plants and cyanobacteria in surface and groundwater and advising for a safe disposal of the unused medicine or waste materials.

Section 4.5 Special precautions for use Other precautions "Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms".

Section 5.3 Environmental properties: Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms".

Section 6.6. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products:
This veterinary medicinal product is dangerous for aquatic organisms (such as cyanobacteria). Do not contaminate surface waters or ponds with used product or containers.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	logKow <0.3	not B
Persistence	$DT_{50,\ compartment,\ 10\ °C}$	27.4 d	not P
Toxicity	NOEC or CMR	0.046 mg/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 for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, and bioequivalence with the reference product has been demonstrated.

MRLs

The active substance florfenicol is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010. The marker substance is sum of florfenicol and its metabolites measured as florfenicol-amine.

MRLs are listed below:

Animal Species	MRL	Target Tissues	Other Provisions
Bovine, ovine, caprine	200 µg/Kg 3000 µg/Kg 300 µg/Kg	Muscle Liver Kidney	Nor for animals from which milk is produced for human consumption. Nor for animals from which eggs are produced for human consumption.
Porcine	300 µg/Kg 500 µg/Kg 2000 µg/Kg 500 µg/Kg	Muscle Skin and fat Liver Kidney	
Poultry	100 µg/Kg 200 µg/Kg 2500 µg/Kg 750 µg/Kg	Muscle Skin and fat Liver Kidney	
Fin fish	1000 µg/Kg	Muscle and skin in natural proportions	
All other food producing species	100 µg/Kg 200 µg/Kg 2000 µg/Kg 300 µg/Kg	Muscle Fat Liver Kidney	

No MRLs are required for the excipients, as indicated in table I of the annex to Commission Regulation 37/2010*.*

Withdrawal Periods

The same withdrawal periods than the reference products are proposed:

Meat and offal

Cattle: IM use (20 mg/kg bodyweight, twice): 30 days.

SC use (40 mg/kg bodyweight, once): 44 days.

Sheep: 39 days.

Pig: 18 days.

Milk

Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13.1, 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.

IV.A Pre-Clinical Studies

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, pharmacodynamics, pharmacokinetics and tolerance studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, clinical 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

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