MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

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

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

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0410/001/DC
Name, strength and pharmaceutical form	Florfeksyl 300 mg/ml solution for injection for cattle, sheep and pigs
Applicant	Laboratorios Karizoo, S.A. Polígono Industrial La Borda Mas Pujades, 11-12 Caldes De Montbui (Barcelona)
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	cattle, sheep and pigs
Indication for use	Treatment of respiratory tract infections in cattle due to Mannheimia haemolytica, Pasteurella multocida and Histophilus somni susceptible to florfenicol. Treatment of ovine respiratory tract infections due to Mannheimia haemolytica and Pasteurella multocida susceptible to florfenicol. Treatment of acute outbreaks of swine respiratory disease caused by strains of 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	29/06/22
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	IT, PL, 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) and the excipients N-methylpyrrolidone, propylene glycol and macrogol 300. This product is a clear yellow solution, free from visible particles.

The veterinary medicinal product is presented in (COEX) PP/HV/EVOH/HV/PP vials of 100 and 250 ml closed with a bromobutyl rubber stopper and sealed with an aluminium/plastic flip-off cap packed individually in carboard box.

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 sites 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 (30 months) 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, and bioequivalence with a reference product has been demonstrated, results of safety tests are not required.

The safety aspects of this product is/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) were provided according to the CVMP/VICH guidelines.

The initial predicted environmental concentration in soil is less than 100 µg/kg for cattle or sheep

A Phase II ERA is required for Weaner Pigs as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 130.3 µg/kg) 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).

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105 (flask)	1.04817 g/l	-
Dissociation constants in water pKa	Open scientific literature Zhao et al. (2015) Batrawi N. (2017)	pKa = 10.73	-
n-Octanol/Water Partition Coefficient logP_{ow}	Open scientific literature Johannes J. (2013)	Log Pow = 0.127	-

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Refesol 01-A: Koc = 29.4 l/kg Refesol 03-G: Koc = 14.9 l/kg Refesol 06-A: Koc = 21.9 l/kg	-
Aerobic Transformation in Soil	OECD 307	Refesol 01-A: $DT_{50\ soil,\ [SFO],\ [20ºC]}$ = 14 d Refesol 02-A: $DT_{50\ soil,\ [SFO],\ [20ºC]}$ = 5.2 d Refesol 03-G: $DT_{50\ soil,\ [SFO],\ [20ºC]}$ = 3.8 Refesol 06-A: $DT_{50\ soil,\ [SFO],\ [20ºC]}$ = 8.8 Refesol 06-A: $DT_{50\ soil,\ [SFO],\ [10ºC]}$ = 27.4 **$DT_{50\ soil}$ geometric mean (20°C): 7.95 d** Mineralisation: Refesol 01-A: 33.3% Refesol 02-A: 52.3 % Refesol 03-G: 53.8 % Refesol 06-A (20ºC): 13.2 % Refesol 06-A (10ºC): 36.8 % Bound residues (after acid and base extraction): Refesol 01-A: 38.2% Refesol 02-A: 37.8 % Refesol 03-G: 31 % Refesol 06-A (20ºC): 35.5 % Refesol 06-A (10ºC): 41 % Relevant metabolites: None	Laboratory studies
Transformation in Manure (species)		% parent (28 d) = 1.4 % % Transformation products (≥ 10%) = NIR 1 TLCstart (28d) = 57.7 %	

Environmental fate			
		NIR 1 TLCstart (59d) = 45.8 % % NER (14 d) = difference between non-sterile sample (31.8%) and sterile sample (17.3%) = 14.5 % % Mineralised (100d) = 3.9 % DT_{50} (FOMC; 20ºC) = 0.18 d.	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	**72h EC_{50} (growth) = 0.24 mg/l**	µg/l	
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	EC10 or NOEC	72h NOEC (growth) = 0.021 mg/L 72h EC10 (growth) = 0.19 mg/L	µg/l	*Tier B*
Daphnia sp. immobilisation	OECD 202	EC50	**48h EC_{50} > 100 mg/l**	µg/l	
Fish, acute toxicity/*species*	OECD 203	LC50	**96h LC_{50} > 100 mg/l**	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	≤ 25% of control at 0.434 mg/kg	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	*Hordeum vulgare* EC50 (biomass)= 1,80 µg/kg *Avena sativa* EC50 (biomass)= 2.15 µg/kg *Brassica napa* EC50 (biomass)= 0.33 µg/kg	µg/kg	

Terrestrial Plants, growth test	OECD 208	EC10 or NOEC	*Allium cepa* EC_{50} (growth) = 0.76 mg/kg NOEC (growth) = 0.19 mg/kg EC10 (growth) = 0.11 mg/kg *Avena sativa* EC_{50} (growth) = 3.54 mg/kg NOEC (growth) = 0.56 mg/kg EC10 (growth) = 0.10 mg/kg *Triticum aestivum* EC_{50} (growth) = 0.95 mg/kg NOEC (growth) = 0.19 mg/kg EC10 (growth) = 0.15 mg/kg *Phaseolus aureus* EC_{50} (growth) = 1.28 mg/kg NOEC (growth) = 0.19 mg/kg EC10 (growth) = 0.30 mg/kg *Raphanus sativus* EC_{50} (growth) = 1.26 mg/kg NOEC (growth) = 0.56 mg/kg EC10 (growth) = 0.57 mg/kg *Solanum lycopersicum* EC_{50} (growth) = 0.58 mg/kg NOEC (growth) < 0.06 mg/kg EC10 (growth) = 0.03 mg/kg *Brassica napus* EC_{50} (growth) = 0.23 mg/kg NOEC (growth) = 0.04 mg/kg EC10 (growth) = 0.06 mg/kg *Beta vulgaris* **EC_{50} (growth) = 0.13 mg/kg** **NOEC (growth) = 0.02 mg/kg** **EC10 (growth) = 0.01 mg/kg**	µg/kg	*Tier B*
Terrestrial plants growth, extended OECD TG 208 (manure spiked with florfenicol). *Brassica napa* most sensitive specie	EMA/CVMP/ ERA/689041/ 2015	EC50 NOEC	EC_{50} = 6780 µg florfenicol/kg soil+manure NOEC = 4420 µg florfenicol/kg soil+manure	µg/kg	
Earthworm/*Enchytraeidae* reproduction	OECD 222	EC10 or NOEC	Tier A endpoint NOEC (mortality) > 1000 mg/kg NOEC (biomass) = 62.5 mg/kg **NOEC (reproduction) = 62.5 mg/kg** **EC50 (reproduction) = 115.5 mg/kg**	µg/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)

Tier A: Risk is identified for cyanobacteria and terrestrial plants and for the groundwater.

Refinement Tier A: Manure degradation was considered and then PECsoil,initial =95.64 ug/kg soil. Consequently, risk of concern was recalculated, for groundwater PECgw was further refined and risk discarded. For surface water, PECsw was recalculated using FOCUS SW.

Risk could not be discarded for terrestrial plants. Therefore Phase II proceeded to Tier B.

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	2.4 ug/L	40.6 ug/L (D2)	>1
groundwater		1.24 ug/L	
	1.9 ug/L (cyanob)	1.24 ug/L	0.65
	30 ug/L (MTCdw)	1.24 ug/L	0.04
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	442 ug/kg (FF+manure, *B. napus*)	130.3 µg/kg	0.29

The risk characterisation resulted in risk quotients (RQs) below 1 for the groundwater and soil compartments 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 indicate that a risk for the environment is indicated and that the following information for special precautions for the protection of the environment were indicated in the texts:
Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms.

The following information has been included under point “environmental properties” of the SPC: Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms and under point 5.5: The veterinary medicinal product should not enter watercourses as florfenicol might be dangerous for aquatic organisms.

PBT assessment

PBT-assessment

Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	BCF	log Pow <4	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	<120 d	not P
Toxicity	NOEC or CMR	Not procedent as no B and no P (only Environment assessment)	T/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, 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.

Tolerance in the Target Species of Animals

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

Resistance

Adequate warnings and precautions appear on the product literature.

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