MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CENFLOX 200 mg/ml solution for use in drinking water for chickens, turkeys and rabbits

CORREO ELECTRÓNICO

mresvet@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0369/001/MR
Name, strength and pharmaceutical form	CENFLOX 200 mg/ml solution for use in drinking water for chickens, turkeys and rabbits
Applicant	CENAVISA S.L. Camí Pedra Estela s/n 43205 Reus (SPAIN)
Active substance(s)	Enrofloxacin
ATC Vet code	QJ01MA90
Target species	Chickens, turkeys and rabbits
Indication for use	Chickens Treatment of infections caused by the following bacteria susceptible to enrofloxacin: *Mycoplasma gallisepticum,* *Mycoplasma synoviae,* *Avibacterium paragallinarum,* *Pasteurella multocida.* Turkeys Treatment of infections caused by the following bacteria susceptible to enrofloxacin: *Mycoplasma gallisepticum,* *Mycoplasma synoviae,* *Pasteurella multocida.* Rabbits For the treatment infectious diseases due to *Pasteurella multocida* and bacterial enteritis due to infection with *E.coli.* Enrofloxacin should be used where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the active substance of choice.

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	Mutual Recognition application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23/10/2019
Date product first authorised in the Reference Member State (MRP only)	30/10/2015
Concerned Member States for original procedure	BG, HR, CZ, HU, LV, LT, PT, RO

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 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 enrofloxacin (200 mg/ml) as active substance and potassium hydroxide and purified water as excipients.

The container/closure system consists in bottles and barrels of high density polyethylene, closed with a polyethylene screw cap and disc for thermo induction.

The choice of the formulation is justified.

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 enrofloxacin, 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.

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

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 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 (3 years), when stored under the approved conditions.

The claim of a 6 months stability after the first opening is based on the demonstration of stability for different batches stored at a temperature of 25 ± 2 ºC and 60 ± 5 % humidity for 6 months.

The claim of a 24 hours stability after reconstitution is based on the demonstration of stability for different batches diluted according to directions.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

As this is an hybrid application according to Article 13.3, the applicant does not provided any data on pharmacological studies, toxicology or other requirements of this veterinary medicinal product. The safety aspects of this product are identical to the reference product.

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

III.A Safety Testing

Pharmacological Studies

In accordance with the requirements for this type of application (article 13.3), no data were supplied for this section, as these were not required.

Toxicological Studies

In accordance with the requirements for this type of application (article 13.3), no data were supplied for this section apart from a user risk assessment, as these were not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The user warnings proposed are in accordance with those of the reference product.

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

Environmental Risk Assessment

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, obtaining the following PEC values

Cattle:

Category	PEC µg active substance/kg soil
Calves	142.8
Cattle (0-1yr)	125.93
Cattle (>2 yr)	145.71

Poultry

Category	PEC µg active substance/kg soil
Poultry	443.48

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		300 mg/L (25ºC, pH= 7.32)	
Dissociation constants in water pKa		pKa1= 5.94 pKa2= 8.70	
n-Octanol/Water Partition Coefficient logP_{ow}		Log Kow= 3.47 (pH= 7)	

<table>
<tr><td colspan="4">Environmental fate</td></tr>
<tr><td>Soil Adsorption/Desorption</td><td>Following principles of OECD 106</td><td>
<table>
<tr><th>clay</th><th>Corg</th><th>Soil type</th><th>pH</th><th>Koc</th><th>Kd</th></tr>
<tr><td>41.7</td><td>1.63</td><td>Ferralsol</td><td>4.9</td><td>186342</td><td>3037</td></tr>
<tr><td>17.2</td><td>0.73</td><td>Cambisol</td><td>5.3</td><td>768740</td><td>5612</td></tr>
<tr><td>7.2</td><td>1.23</td><td>Podsol</td><td>6.0</td><td>99975</td><td>1230</td></tr>
<tr><td>23.4</td><td>1.58</td><td>Leptosol</td><td>7.5</td><td>16506</td><td>260</td></tr>
<tr><td>2.5</td><td>0.70</td><td>Flurisol</td><td>5.3</td><td>70914</td><td>496</td></tr>
</table>
</td><td></td></tr>
<tr><td>Aerobic and Anaerobic Transformation in Soil</td><td>OECD 307</td><td>
<table>
<tr><th>Soil</th><th>DT_{50} enroflox (d)</th><th>DT_{90} enroflox (d)</th></tr>
<tr><td>Refesol 01-A</td><td>141</td><td>469</td></tr>
<tr><td>Refesol 02-A</td><td>103</td><td>342</td></tr>
<tr><td>Refesol 03-G</td><td>99</td><td>330</td></tr>
<tr><td>Refesol 04-A</td><td>149</td><td>495</td></tr>
</table>
(20ºC, SFO kinetics)

DT50 geomean= 120.9 d (20º)

Worst case (149 d at 20ºC converted to 227 at 12ºC) (Arrhenius correction)

DT50 arithmetic mean=123 d
</td><td></td></tr>
</table>

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*species*		EC50	(Cianobacteria; *M.aeruginosa*) EC50 =49 µg/l (Algae: *P.subcapitata*) EC50 = 3100 µg/l	µg/l	*Nominal concentration for cianobacteria* *Static*
Daphnia sp. immobilisation		NOEC	NOEC= 10 mg/kg	mg/l	EPA test 48h
Daphnia magna, reproduction		EC10 or NOEC	EC50 (24h)= 131.7 mg/L EC50 (48h)= 56.7 mg/L EC50 (21d)= 11.47 mg/L NOEC= 5 mg/L	mg/l	EPA 821-R-02-012 *EPA guidance*
Fish, acute toxicity/*species*		NOEC	*P. promelas* NOEC= 10 mg/kg	mg/l	
		EC50	*O. latipes*	mg/l	

			EC50>100 mg/L		
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	No effects at the highest concentration 29 mg/kg. Control deviation <25% OECD 216		Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	species / EC50 (growth) / NOEC *C. sativus* / 204 / <10 *L. sativa* / 435 / 100 *P. aureus* / 343 / 31.6 *A. sativa* / 323 / 100 *T. aestivum* / 190 / 31.6 *S. cerealis* / 124 / 48	mg/kg	
Earthworm	OECD 222	EC10 and EC50	EC10= 45.53 mg/kg EC50= 5796.54 mg/kg LC50>1200 mg/kg	mg/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	0.49 µg/L (cyanobacteria, worst case)	PECSurface water= 0.0649 / 3= 0,0216 µg/L	0.044
groundwater	0.1 µg/L	PECgroundwater= 0.0649 µg/L	No risk
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	-	-
soil	1240 µg/kg (plants, worst case)	PECsoil,plateau (chicken)= 508.49 µg/kg	0.41

dung	-	-	-

The risk characterisation resulted in risk quotients(RQs) below 1 for the surface water, groundwater, soil and dung 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	The "B" criterion is not complied (EMA/CVMP/ERA/52740/2012)	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	227.6 d	vP
Toxicity	NOEC or CMR	-	T/not T
PBT-statement :	The compound is considered as vP		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this application is in accordance with Article 13(3) and the applicant shall not be required to provide the results of residues tests because all these data are in the documentation that supports the marketing authorization of the reference product.

MRLs

Enrofloxacin is listed in the Annex of the Commission Regulation (EU) No 37/2010 (enrofloxacin). The marker substance is the sum of enrofloxacin and ciprofloxacin.

MRLs are listed below:

	Rabbits	Poultry
Muscle	100 µg/kg	100 µg/kg
Liver	200 µg/kg	200 µg/kg
Kidney	300 µg/kg	300 µg/kg
Fat / skin	100 µg/kg	100 µg/kg

The excipients are included in table 1 of Commission Regulation (EU) 37/2010 (No MRL required) or in the list of substances considered as not falling within the scope of Council Regulation (EC) No. 470/2009.

Withdrawal Periods

The withdrawal periods agreed for the reference product can be applied to the CENFLOX 200 mg/ml solution for use in drinking water for chickens, turkeys and rabbits, as follows:

Chickens: Meat: 7 days
Turkeys: Meat: 13 days
Rabbits: Meat: 3 days

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

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

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