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PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MOXODEX LA 100 MG/ML SOLUTION FOR INJECTION FOR CATTLE

Date: 12 June 2023

PRODUCT SUMMARY

EU procedure number	FR/V/0452/001/DC
Name, strength and pharmaceutical form	MOXODEX LA 100 MG/ML SOLUTION FOR INJECTION FOR CATTLE
Applicant	CHANELLE PHARMACEUTICALS MANUFACTURING LIMITED, IDA INDUSTRIAL ESTATE, H62 FH90 LOUGHREA IRELAND
Active substance(s)	Moxidectin
ATC vetcode	QP54AB02
Target species	Cattle
Indication for use	In cattle weighing from 100 to 500 kg body weight, treatment and prevention of mixed infestations by the following gastro-intestinal nematodes, respiratory nematodes and certain arthropod parasites: ***Adult and immature gastro-intestinal nematodes:*** *. Haemonchus placei* *. Haemonchus contortus* *. Ostertagia ostertagi* (including inhibited larvae) *. Trichostrongylus axei* *. Trichostrongylus colubriformis* *. Nematodirus helvetianus* (adults only) *. Nematodirus spathiger* *. Cooperia surnabada* *. Cooperia oncophora* *. Cooperia pectinata* *. Cooperia punctata* *. Oesophagostomum radiatum* *. Bunostomum phlebotomum* (adults only) *. Chabertia ovina* (adults only) *. Trichuris* spp. (adults only) ***Adult and immature respiratory tract nematode*** *. Dictyocaulus viviparus* ***Warble grubs (migrating larvae)*** *. Hypoderma bovis* *. Hypoderma lineatum* ***Lice*** *. Linognathus vituli* *. Haematopinus eurysternus* *. Solenopotes capillatus* *. Bovicolabovis* (aid in control) ***Mange mites*** *. Sarcoptes scabiei* *. Psoroptes ovis* *. Chorioptes bovis* (aid in control)

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 13(1)** of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	05/04/2023
Concerned Member States for original procedure	Belgium, Ireland, Poland, Portugal, Spain

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 (physicochemical, biological or microbiological information)

A. Product description

The VMP contains 100 mg moxidectin per mL and the excipients benzyl alcohol, butylhydroxytoluene, sorbitan oleate and propylene glycol dicaprylocaprate.

The container/closure system is high density polyethylene vials with chlorinated butyl rubber stopper sealed with aluminium cap presented in 50 and 250 mL.

The choice of the formulation and presence of preservative are 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 a licensed manufacturing site.

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

A post-authorisation commitment has been provided to validate the manufacturing process for full-scale batches.

C. Production and control of starting materials

The active substance is moxidectin, an established active substance described in the European Pharmacopeia. 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.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 site have been provided demonstrating compliance with the specification.

F. Stability tests

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 VMP throughout its shelf life when stored under the approved conditions.

3. SAFETY DOCUMENTATION (safety and residues tests)

A. Safety tests

Pharmacological studies

As this is a generic application according to **Article 13(1)** of Directive 2001/82/EC as amended and bioequivalence with CYDECTINE 10 % LA POUR BOVINS, marketed by ZOETIS France, which has been authorized in France since 17/01/2005 (reference VMP) has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this VMP are identical to the reference VMP.

Toxicological studies

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application), and therefore specific toxicological data on safety relating to the active substance are not required.

User safety

The applicant has provided a user safety assessment broadly in compliance with the relevant guideline.

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

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 VMP is an endoparasiticide for cattle and the target animals are reared on pasture.

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	Published reference	31.4 mg/L	
Dissociation constants in water pKa	Published reference	pKa <2	

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
n-Octanol/Water Partition Coefficient logP_{ow}	Published references	>6 5.4	theoretical potential for bioaccumulation

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Mean Kfoc = 18850 (22390 (pH 5.36), 17026 (pH 5.51), 19994 (pH 6.95), 18619 (pH 7.37), 16223 (pH 7.25)) in Sand (0.59), sandy loam (1.57), sandy loam (1.23), loam (2.02) and clay loam (1.82) soils (OC%) respectively	
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 20°C,\ DFOP}$ = 13.8, 35.0 and 87.3 days in sand (0.73), sandy loam (0.69), and clay (1.84) soils (OC%) respectively (%NER 29.2, 28.3 and 21.9) $DT_{50,\ 12°C\ worst\ case.}$ = 185 days Transformation products >10%: metabolites M2b and M3	

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks
Algae growth inhibition test/ *Pseudokirchneriella subcapita*	OECD 201	EC50	>29100 (m)	µg/l	
Daphnia sp. immobilisation	OECD 202	EC50	0.263 (n)	µg/l	
Fish, acute toxicity/ *Oncorhynchus mykiss*	OECD 203	LC50	0.849 (n)	µg/l	
Earthworm reproduction	OECD 222	EC10	420	µg/kg	
Dung fly larvae/species	OECD 228	EC50	1470	µg/kg_{dw}	
Dung beetle larvae/species	OECD GD 122	EC50	3630	µg/kg_{dw}	
Bioaccumulation in fish/ *Oncorhyncus mykiss*	OECD 305 Type:	BCF_{SSL} BCF_{kLg}	2635 3048	l/kg	% lipids: 5

(n) nominal, (m) measured

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:

Tier A

Soil	**Moxidectin**		
	PEC	**PNEC**	**RQ**
Dung fly larvae	25.4 mg/kg_{wwt}	0.0021 mg/kg_{wwt}	**12095**
Dung beetle	25.4 mg/kg_{wwt}	0.0145 mg/kg_{wwt}	**1752**
Earthworm, 56 d	0.00627 mg/kg_{dwt}	0.042 mg/kg_{dwt}	0.15

Surface water, run off/drainage	**Moxidectin**		
	PEC	**PNEC**	**RQ**
Algae, growth inhibition, 72 h	0.00018 µg/l	>291 µg/l	<6.39x 10^{-7}
Daphnia, acute, 48 h	0.00018 µg/l	0.000263 µg/l	0.71
Fish, acute, 96 h	0.00018 µg/l	0.000849 µg/l	0.22

Surface water, direct excretion	**Moxidectin**		
	PEC	**PNEC**	**RQ**
Algae, growth inhibition, 72 h	1.05 µg/l	>291 µg/l	0.004
Daphnia, acute, 48 h	1.05 µg/l	0.000263 µg/l	**3992**
Fish, acute, 96 h	1.05 µg/l	0.000849 µg/l	**1237**

Sediment, direct excretion	**Moxidectin**		
	PEC	**PNEC**	**RQ**
Based on *D. magna* endpoint	12.38 µg/l	0.248 µg/l	**50**

Tier A refined (direct excretion)

Surface water, direct excretion	**Moxidectin**			
	PEC	**PNEC**	**RQ**	**Trigger**
Daphnia, acute, 48 h	Step 2: 0.0038 µg/l	0.000263 µg/l	14.4	1
Fish, acute, 96 h	Step 2: 0.0038 µg/l	0.000849 µg/l	4.5	1

Sediment, direct excretion	**Moxidectin**			
	PEC	**PNEC**	**RQ**	**Trigger**
Based on *D. magna* endpoint	Step 2: 3.59 µg/kg_{dwt}	0.248 µg/l	14.5	1

Secondary poisoning

Via the aquatic food chain

	Moxidectin			
	$PEC_{oral, predator}$	**$PNEC_{oral}$**	**RQ**	**Trigger**
Fish-eating predators	0.0989 mg/kg_{wwt} (based on calculated BCF_{fish})	0.13 mg/kg_{food}	0.76	1
Fish-eating predators	0.0506 mg/kg_{wwt} (Step 3 PEC_{sw} refinement)	0.13 mg/kg_{food}	0.39	1

Via the terrestrial food chain

	Moxidectin			
	$PEC_{oral, predator}$	**$PNEC_{oral}$**	**RQ**	**Trigger**
Earthworm-eating predators	0.0108 mg/kg_{wwt}	0.13 mg/kg_{food}	0.083	1

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	2635 l/kg	B
Persistence	$DT_{50,\ soil,\ 12\ °C}$	185 days	vP
Toxicity	NOEC	<0.01 mg/l	T
PBT-statement:	The compound is considered as PBT		

Conclusion

According to RQs values, a risk cannot be ruled out for dung fauna and aquatic organisms. Furthermore, moxidectin fulfils PBT criteria. Consequently, the SPC has been amended to take into account the Commission Decision concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for veterinary medicinal products containing moxidectin to be administered orally, topically or subcutaneously to cattle, sheep and horses.

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

B. Residues documentation

Residue tests

No residue depletion studies were conducted on the basis that bioequivalence with the reference product has been demonstrated.

Maximum Residue Limits

Moxidectin, is included in table 1 of the annex of the Commission Regulation (EU) No. 37/2010, as follows,

MOXIDECTIN						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
moxidectin	Bovine, ovine, *Equidae*	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	No entry	Antiparasitic agents/ Agents against endo- and ectoparasites	37/2010 of 22.12.2009
	Bovine, ovine	40 µg/kg	Milk			

An acceptable daily intake (ADI) was defined for moxidectin. It is 3 µg/kg bw (*i.e*. 210µg/person).

Withdrawal Periods

Based on the data provided above, a withdrawal period of 108 days for meat and offal in cattle is justified. The product is not permitted for use in lactating animals producing milk for human consumption or industrial purposes or within 80 days of expected parturition.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to **Article 13(1)** of Directive 2001/82/EC as amended and bioequivalence with a reference VMP has been demonstrated according to section 7.1 of the European bioequivalence guideline (Guideline on the conduct of bioequivalence studies for veterinary medicinal products EMA/CVMP/EWP/16/2000), efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

No pre-clinical studies such as dose determination, dose confirmation and target animal tolerance studies, were performed.

As this is a generic application according to **Article 13(1)** of Directive 2001/82/EC as amended and bioequivalence with CYDECTINE 10 % LA POUR BOVINS, marketed by ZOETIS France, which has been authorized in France since 17/01/2005 (reference VMP) has been demonstrated, results of pre-clinical studies are not required.

The administration routes and dosage for this VMP are the same as those of the reference VMP.

Therefore, it is accepted that the target animal safety profile of the proposed product will be the same as that of the reference product and no specific study is required. The product literature accurately reflects the type and incidence of adverse effects, which might be expected.

Regarding development of resistance and related risk in animals, adequate warnings and precautions appear on the product literature.

B. Clinical trials

No clinical trials were performed. The indications of the reference VMP in the target species cattle apply to this VMP.

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.