MINISTERIO DE SANIDAD
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)

DECENTRALISED PROCEDURE

[DRAFT]PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Moxisolv LA 100 mg/ml Solution for Injection for Cattle

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/0413/001/DC
Name, strength and pharmaceutical form	Moxisolv LA 100 mg/ml Solution for Injection for Cattle
Applicant	Bimeda Animal Health Limited 2,3&4 Airton Close Airton Road Tallaght Dublin 24
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
Bovicola bovis (reduction of infestation)

Mange mites:
Sarcoptes scabiei
Psoroptes ovis
Chorioptes bovis (reduction of infestation)

Moxidectin has a persistent action and protects cattle for a certain duration against
infection or re-infection with the following parasites for the period indicated:

Species:	**Protection period (days):**
Dictyocaulus viviparus	120
Ostertagia ostertagi	120
Haemonchus placei	90
Oesophagostomum radiatum	150
Trichostrongylus axei	90
Linognathus vituli	133

The veterinary medicinal product is effective against *Hypoderma* larvae at the time of treatment but its persistent activity against *Hypoderma* has not been evaluated. If the veterinary medicinal product is given before the end of the fly season complimentary treatment with a product effective against *Hypoderma* may be required.

Persistent efficacy periods have not been established for parasite species other than those included in the above list. Therefore, re-infection of animals on pasture contaminated by parasites other than these remains possible before the end of the 90-day minimum persistency period demonstrated for specific species.

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	23/11/22
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	CMS: AT, BE, CZ, DE, EE, FR, IE, IT, LT, LV, NL, PL, PT, SK, UK(NI)

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 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 moxidectin (100 mg) and benzyl alcohol, sorbitan oleate and propylene glycol dicaprylocaprate.

The container/closure system is HDPE bottles, closed with a type I grey chlorobutyl rubber stopper, and sealed with an aluminium overseal.

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.

The product is manufactured using conventional manufacturing techniques. The test performed during production are described. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is moxidectin for veterinary use, an established active 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.

Certificate 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.

The excipients are in conformity with Ph.Eur. requirements. No excipients are within the scope of the TSE Guideline present or used in the manufacture of this product.

The glass vials and stoppers are in conformity with the Ph.Eur. requirements.

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 over 36 months 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 (no special storage conditions are required).

An in-use shelf-life of 28 days has been supported by appropriate data and is considered acceptable.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

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 and residue 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 consumers.

III.A Safety Testing

Pharmacological Studies

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

Toxicological Studies

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

User Safety

A brief user safety assessment has been presented. Since the candidate product has the same composition in active substances and excipients than the reference product, it is assumed that the risks for the user will be similar to those associated with the use 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

Examples (The order reflects the stepwise assessment):

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines**. Phase I-Indoor uses**: All values are below the trigger value of 100 µg/kg; therefore, no further risk assessment is required for animals reared indoors. **Phase I-Pasture:** $PEC_{soil,initial}$ was below 100 µg/kg, but the risk assessment should proceed to phase II to address specific concerns according to VICH GL6 guideline.

A Phase II ERA is required as the product is an ectoparasiticide 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). The data were considered complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	0.47 mg/L (at 20°C ± 0.5°C)	Valid study
Dissociation constants in water pKa	OECD 112	pKa = No dissociation constant at 20ºC could be determined in the pH range of 1 to 13.	Valid study (spectrophotometric method)
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 123	logK_{ow} =7.08	Valid study

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Refesol 02-A: Koc = 65912 cm^3/g pH 5.93 Refesol 03-G: Koc = 16604 cm^3/g pH 5.86 Refesol 04-A: Koc = 21898 cm^3/g pH 5.22 Lufa 2.2: Koc = 39916 cm^3/g pH 6.00 Lufa 5M: Koc = 32702 cm^3/g pH 6.96 GeoMean Koc absorption = 31554 cm^3/g	
Aerobic and Anaerobic Transformation in Soil	OECD 307	<u>Persistence DT50: (at D 120 LOQ)</u> All DT50 from laboratory studies, normalized at pF2 and 20ºC Refesol-01-A $DT50_{20ºC,\ FMOC}$=31.5 d Refesol-02-A $DT50_{20ºC,\ FMOC}$=44.1 d Refesol-03-G $DT50_{20ºC,\ HS,\ k2}$=76.65 d Refesol-05-G $DT50_{20ºC,\ HS,\ k2}$=34.6 d <u>Modelling DT50 (at D120 LOQ)</u> Refesol-01-A $DT50_{20ºC,\ SFO}$=19.7 d Refesol-02-A $DT50_{20ºC,\ SFO}$=29.2 d Refesol-03-G $DT50_{20ºC,\ SFO}$=47 d Refesol-05-G $DT50_{20ºC,\ SFO}$=25.5 d	

Environmental fate			
		Geomean DT50 for modelling (at RMS D70 report)=30.24d Mineralisation: Refesol 01-A: 26.8 % Refeso 02-A: 28.9 % Refesol 03-G: 11.9 % Refesol 05-G: 17.6 % Bound residues: Refesol 01-A: 26.8 % Refeso 02-A: 15.8 % Refesol 03-G: 21.1 % Refesol 05-G: 21.1 %	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae *Desmodesmus subspicatus*	OECD 201	EC50	48h ErC50 = 470 µg/$L_{(nm)}$ 48h ErC_{10} = 100.7 µg/$L_{(nm)}$	µg/l	
Daphnia sp. immobilisation	OECD 202	EC50	48h EC_{50} = 0.958 µg/$L_{(mm)}$	µg/l	
Daphnia magna, reproduction	OECD 211	EC10 or NOEC	21d EC_{10} = 0.00616 µg/$L_{(mm)}$	µg/l	*Tier B*
Fish, acute toxicity *O. mykiss*	OECD 203	LC50	72h EC_{50}= 0.621 µg/$L_{(mm)}$	µg/l	
Earthworm reproduction	OECD 222	EC10 or NOEC	$NOEC_{28d}$ (mortality&biomass) = 1.7 mg/kg $NOEC_{56d}$ (reproduction) = 0.59 mg/kg EC10 reproduction = 0.63 mg/kg EC50 reproduction = 1.6 mg/kg	µg/kg	
Sediment dwelling *C. riparius*	OECD 218/219	NOEC or EC10	28d EC50 = 7 $µg_{(mm)}$ /kg sediment dw 28d EC10 = 2.74 $µg_{(mm)}$ /kg sediment dw	µg/kg	*Tier B*
Dung fly larvae *Scatophaga stercoraria*	OECD 228	EC50	Emergence: NOEC = 1 mg/kg, EC10 = 0.86 mg/kg, EC50 = 1.71 mg/kg dw (equivalent to 246.68 µg/kg fresh weight) Development: NOEC >= 3.2 mg/kg	µg/kg	

Musca autumnalis			LC50 = 70.4 µg/kg fresh weight		Blanckenhorn, 2013 Scientific article
Dung beetle larvae *Aphodius constans*	OECD GD 122	EC50	LC_{50} = 5400 µg/kg dw LC50 = 3375 µg/kg fresh weight (Corrected with 60% moisture)	µg/kg	Hempel, 2006 Scientific article
Bioaccumulation in fish *O. mykiss*	OECD 305	BCF	4380	l/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	$PNECsw_{fish,\ tier\ B}$ = 0.000621µg/L $PNECsed_{invertebrate,\ tier\ B}$ = 0.274 µg/kg	Tier B PECsw=0.0036 µg/L PECsed=7.48 µg/L	6 (Daphnia) 27 (sediment dwelling)
Groundwater (since PEC<0.1 but PNEC<1 ug/L)	PNECgw= 6.21E-5 µg/L (acute, fish)	<0.000000 µg/L	<1
soil microorganisms: Nitrogen transformation test	NA (ectoparasiticide pasture scenario)	NA	NA
Soil (earthworm, ectoparasiticide pasture scenario)	63 µg/Kg	4.18 µg/kg	0.07
dung Flies Beetles	 0.704 µg/Kg (*M. autumnalis*) 34 µg/Kg	15200 µg/kg	21714 (fly larvae)

The risk characterisation resulted in risk quotiens (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, sediment and dung compartments indicate that a risk for the environment is indicated and that risk mitigation measures are required for this product, according to the referral procedure of 26/09/2017 under Article 35 of Directive 2001/82/EC (EMEA/V/A/116) for Moxidectin. The texts accompanying the product should strictly adhere to the agreed in the Annex III of the referral.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	4380	B
Persistence	Worst case, best fit, k_2 (slow phase) $DT_{50, soil, 12\ °C}$	163 d	P
Toxicity	NOEC or CMR	21d $EC_{10,daphnia}$ = 0.00616 µg/$L_{(mm)}$ NOEC $_{daphnia}$=0.003 µg/$L_{(mm}$	T
PBT-statement :	The compound is considered as PBT		

III.B Residues documentation

Residue Studies

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

MRLs

The active substance moxidectin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010.

MRLs are listed below:

Pharmacologically active substance(s)	**Marker residue**	**Animal species**	**MRLs (µg/kg)**	**Target tissues**

Moxidectin	Moxidectin	Bovine, ovine and equidae	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney
		Bovine, ovine	40 µg/kg	Milk

Withdrawal Periods

The same withdrawal periods as the reference product are proposed:

Meat and offal: 108 days.

Milk: Not authorised for use in animals producing milk for human consumption. Do not use in pregnant animals which are intended to produce milk for human consumption within 80 days of expected parturition.

The withdrawal period is based solely on a single injection at the ear site of injection.

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(pharmaceuticals only)

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