IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Moxodex 5 mg/ml Pour on solution for cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0404/002/MR
Name, strength and pharmaceutical form	Moxodex 5 mg/ml pour on solution for cattle
Active substance(s)	Moxidectin
Applicant	Chanelle Pharmaceuticals Manufacturing Limited
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	18 November 2020
Target species	Cattle
Indication for use	Infections of cattle with parasites sensitive to moxidectin. For the treatment of infections caused by: **- Adult and larval gastro-intestinal nematodes:** *Haemonchus placei* *Ostertagia ostertagi* (including inhibited larvae) *Trichostrongylus axei* *Nematodirus helvetianus* *Cooperia oncophora* *Cooperia punctata* (adults) *Oesophagostomum radiatum* (adults) *Bunostomum phlebotomum* (adults) **- Adult respiratory tract nematode** *Dictyocaulus viviparous* **- Warbles (migrating larvae)** *Hypoderma bovis* *Hypoderma lineatum* **- Lice** *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* *Bovicola bovis (Damalinia bovis)* **- Mange Mites** *Sarcoptes scabiei* *Psoroptes ovis* *Chorioptes bovis* - **Horn Flies** *Haematobia irritans* The product has a persistent effect in preventing against reinfection by: *Ostertagia ostertagi* for 5 weeks *Dictyocaulus viviparus* for 6 weeks.
ATCvet code	QP54AB02
Concerned Member States	Finland, France, Sweden

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive

2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars
The product contains 5 mg/ml moxidectin as the active substance and the excipients aromatic solvent, myristal propoxylate propionic ester, polybutene polymer, 2-Tert-butylhydroquinone, butylhydroxyanisole (E320) and medium chain triglycerides,
The container/closure system consists of fluorinated high density polyethylene squeeze-pour packs of 1 L or flexi-packs of 2.5 L, 3 L, 5 L, and 6 L. The 1 L squeeze-pour container includes an integrated dosing device with a measuring scale, graduated each 5 ml up to 25 ml.
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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials
The active substance is moxidectin, 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 has been provided.
Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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.

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability
Stability data on the active substance has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

An exemption from the need to conduct an *in vivo* bioequivalence study in the target species was accepted in accordance with section 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies on the basis that the product has the same pharmaceutical form, contains the same concentration of the active substance and has the same excipients as the reference product Cydectin 0.5% w/v Pour-on for cattle, with the exception of the reference product also containing citric acid and propylene glycol. In addition, the intended target species, route of administration and the proposed posology of the test product are the same as for the reference product.

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

Toxicological Studies

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

User Safety

The applicant has provided a user safety assessment generally in compliance with the relevant guideline which shows that the main risk to the user is local irritation via accidental skin or eye exposure.
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:

The highest initial predicted environmental concentration in soil ($PEC_{soil, initial}$ = 2.91 µg/kg) is less than 100 µg/kg.
A Phase II ERA is required as the product is an ectoparasiticide and 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). The data were considered to be complete and acceptable.

Physical-chemical properties		
Study type	**Test protocol**	**Result**
Water solubility	Published reference	31.4 mg/l
Dissociation constants in water pKa	Published reference	pKa = <2
n-Octanol/Water Partition Coefficient $logP_{ow}$	KOWWIN (estimate)	$logK_{ow}$ 6.70

Environmental fate		
Soil Adsorption/Desorption	OECD 106	Koc = 18,850.4 K_d = 715.2
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50, 20°C}$ = 87.3 days $DT_{50, 12°C. worst case}$ = 185.3 Transformation products >10%: *Metabolites M2b and M3.*

Study type	Test protocol	Endpoint	Result	Unit
Algae, growth inhibition test/*Pseudokirchneriella subcapitata Hindák*	OECD 201	EC_{50}	29,100	µg/l
Daphnia sp. immobilisation	OECD 202	EC_{50}	0.263	µg/l
Fish, acute toxicity/*Oncorhynchus mykiss*	OECD 203	LC_{50}	0.849	µg/l
Earthworm reproduction	OECD 222	NOEC	1,030	µg/kg
Dung fly larvae/ *Musca autumnalis* De Geer	OECD 228	EC_{50}	1,470	µg/kg dry wt.
Dung beetle larvae/ *Aphodius constans*	OECD GD 122	LC_{50} (21 day)	3,630	µg/kg dry wt.
Dung beetle larvae/*Aphodius constans*	OECD GD 122	EC_{50} (70 day)	2,000	µg/kg dry wt.
Bioaccumulation in fish/ *Oncorhyncus mykiss*	OECD 305	$BCF_{lipid\text{-}normalised\ steady\text{-}state}$	2,665	l/kg

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	2,665	B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	185.3 days	(v)P
Toxicity	EC_{50} (*D. magna*)	0.263 µg/l	T
PBT-statement:	The compound is considered as PBT		

In relation to the PBT (persistent, bioaccumulative and toxic) status of moxidectin, as the bioconcentration factor (BCF) in an aquatic species is greater than 2000, moxidectin fulfils the criteria for bioaccumulation and has the potential to bioaccumulate. With a degradation half-life in soil higher than 180 days and acute $E(L)C_{50}$ values in Daphnia and fish studies of <0.01 mg/l, moxidectin is classified as very persistent and toxic. Therefore, moxidectin is concluded to be a PBT substance.

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. The risk quotient (RQ) for each compartment were calculated.
The results of the Phase II Tier A assessment indicated that the product will not present an unacceptable risk for soil microorganisms, terrestrial plants or earthworms.
The assessment of secondary poisoning indicates that there is no concern for fish or earthworm eating predators.
The results of the Phase II Tier B assessment indicated that a risk for aquatic organisms and dung fauna cannot be excluded and that appropriate risk mitigation advice is required for this product.

Conclusion

Based on the data provided in the ERA, a risk to aquatic organisms as well as dung fauna cannot be excluded. As moxidectin has been determined to be a PBT substance, it may have a negative impact on aquatic life when allowed to enter water bodies. Therefore, suitable risk mitigation measures and advice were included in the SPC for this product.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted and their omission was accepted because the product is applied topically and bioequivalence with the reference product is accepted. This was based on the product being the same type of solution, containing the same concentration of the active substance and similar excipients in similar amounts and will be administered to the same target species, using the same route of administration at the same dose rates as already approved for the reference product. Consequently, a similar rate and extent of absorption of the active substance from the application site is expected.

MRLs

Moxidectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissue	Other provisions
Moxidectin	Moxidectin	Bovine, ovine, *equidae*	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	No entry
		Bovine, ovine	40 µg/kg	Milk	

Withdrawal Periods

Based on the information provided above, a withdrawal period of 14 days for meat in cattle and 6 days for milk are justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

An exemption from the need to conduct an *in vivo* bioequivalence study in the target species was accepted in accordance with section 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies on the basis that the product has the same pharmaceutical form, contains the same concentration of the active substance and has the same excipients as the reference product Cydectin 0.5% w/v Pour-on for cattle, with the exception of the reference product also containing citric acid and propylene glycol. In addition, the intended target species, route of administration and the proposed posology of the test product are the same as for the reference product.

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

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, systemic tolerance studies are not required. Evidence to demonstrate target animal tolerance at the administration site is expected for topically-applied products. Given that the product includes the same concentration of active substance and the same excipients in similar amounts as the reference product, no difference in tolerance at the administration site is expected between candidate and reference products.

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

Resistance

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, the resistance profile of the product will be the same as that of the reference product.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, 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 benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

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.

Changes:
None.