Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ovimox 1 mg/ml Oral Solution for Sheep

Date Created: October 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Ovimox 1mg/ml Oral Solution for Sheep
Applicant	EU Pharmaceuticals Ltd 37 Geraldine Road London SW18 2NR
Active substance	Moxidectin
ATC Vetcode	QP54AB02
Target species	Sheep
Indication for use	For the treatment and prevention of infections caused by the following worm species, susceptible to moxidectin: Adult and immature gastro-intestinal nematodes: - *Haemonchus contortus* (including inhibited larvae) - *Teladorsagia circumcincta* (including inhibited larvae) - *Ostertagia trifurcata* - *Trichostrongylus axei* (including inhibited larvae) - *Trichostrongylus colubriformis* - *Trichostrongylus vitrinus* - *Nematodirus battus* - *Nematodirus spathiger* - *Nematodirus filicolis* (adults only) - *Strongyloides papillosus* (larval stages only) - *Cooperia curticei* (adults only)

	- *Cooperia oncophora* - *Oesophagostomum columbianum* - *Oesophagostomum venulosum* (adults only) - *Chabertia ovina* - *Trichuris ovis* (adults only) Adult respiratory tract nematode: - *Dictyocaulus filaria* The product has a persistent effect in preventing reinfection: for 5 weeks by *Teladorsagia circumcincta* and *Haemonchus contortus* for 4 weeks by *Oesophagostomum columbianum* Clinical trials, after experimental and natural infection, have shown that the product is effective against certain benzimidazole resistant strains of: *Haemonchus contortus* *Teladorsagia circumcincta* *Trichostrongylus colubriformis* *Cooperia curticei*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	3rd October 2019

I. SCIENTIFIC OVERVIEW

This was as application for a generic product, Ovimox1 mg/ml Oral Solution for Sheep. The reference product is Cydectin 0.1% w/v oral solution for sheep, marketed in the UK since April 1996. The application was submitted under Article 13 (1) of Directive 2001/82/EC, as amended. The product is an anthelmintic, indicated for use against a range of target organisms as specified above.

The dose rate is 1 ml/5 kg bodyweight, equivalent to 200 µg moxidectin/kg bodyweight. 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, any reactions observed are indicated in the SPC.[1] 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 [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 1 mg/ml moxidectin and the excipients benzyl alcohol, propylene glycol, polysorbate 20 and purified water.

The container/closure system consists of white HDPE flexi containers containing 1L, 2.5 L, 3 L and 5 L of product. The containers are closed with blue polypropylene caps with tamper evident aluminium seals. The particulars of the containers and controls performed are provided and conform to the regulation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The choice of the formulation and the presence of preservative are justified.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple addition and mixing process, followed by suitable sterilisation.

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

II.C. Control of Starting Materials

The active substance is moxidectin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). 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. A Certificate of Suitability was provided.

Excipients and packaging comply with an appropriate Ph. Eur. Certificate of Suitability.

II.C.4. Substances of Biological Origin

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.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product are those for: appearance, identification of active substance, identification of preservative, pH, assay of quantity, uniformity of fill and microbiological quality.

II.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. The retest period of 2 years was accepted. Suitable stability studies on the finished product were also provided.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 6 months.
Keep the container in the outer carton in order to protect from light.
Do not store above 25°C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

As this was an application for a generic product, and bioequivalence with the reference product was accepted, the results of toxicological and pharmacological tests were not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- This product can cause skin and eye irritation.
- Avoid direct contact with skin and eyes.
- Wear impermeable rubber gloves during use.
- In the event of eye contact, flush the eye with copious amounts of clean water and seek medical advice.
- Wash hands or any exposed area after use.
- Do not smoke, eat or drink when handling this product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The product is a parasiticide used in pasture animals and a Phase II ERA was required. (Question 16 VICH decision tree).

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substance, moxidectin, unless indicated otherwise.

Physicochemical properties

Study type	Guideline	Result
Water solubility	OECD 105	31.4 mg/l
Dissociation constants in water pKa	-	pKa <2
Melting Point/Melting Range	-	145 - 154°C
Vapour Pressure	-	4.69×10^{-20}
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	>6

As the log K_{ow} is >4, which suggests that moxidectin could partition to lipid, the potential for bioaccumulation, secondary poisoning and for moxidectin to be a persistent, bioaccumulative and toxic (PBT) substance has been considered in Tier B of the ERA.

Environmental fate

Study type	Result
Soil Adsorption/Desorption (OECD 106)	Range of 5 soils: $K_F^{ads}{}_{oc:}$ 16 223 to 22 390 ml/g
Aerobic and Anaerobic Transformation in soil (OECD 307)	Range of 3 soils: DT_{50} = 13.8 to 87.3 days DT_{90} = 83.4 to 319 days

Using the ASTM mobility classification scheme (ASTM, 2006), moxidectin is classified as being 'immobile' in soil.

The normalisation of the highest DT_{50} value to a temperature of 12°C results in a DT_{50} value of 185.3 days. This is slightly above the trigger value of 180 days; resulting in a classification for moxidectin of very persistent in soil.

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test (*Pseudokirchneriella subcapitata)*	OECD 201	EC_{50}	>29.1 mg/l
Daphnia sp. immobilisation	OECD 202	EC_{50}	0.263 µg/l
Fish, acute toxicity (*Oncorynchus mykiss)*	OECD 203	LC_{50}	0.849 µg/l
Earthworm*/Species* subacute/reproduction	OECD 220/222	NOEC	1.03 mg/kg soil dwt
Dung fly larvae *(Musca autumnalis)*	OECD 228	EC_{50}	1.47 mg/kg dung dwt. (95% confidence interval: 0.907 - 2.37 mg/kg dung dwt)
Dung beetle larvae *(Aphodius constans)*	OECD draft	LC_{50}	3.63 mg/kg dwt

Exposure assessment (Predicted exposure concentration)

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Target animal	PEC			
	Soil (µg/kg)	Dung (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Adult sheep	0.96	8 000	0.0007	0.00023333
Lamb	0.72	8 000	0.0005	0.00016667

As the calculated $PEC_{groundwater}$ values for the target animals are below the trigger value of 0.1 µg/l, a groundwater leaching simulation with FOCUS PEARL is not required.

Risk Characterisation (Risk Quotient)

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows.

Adult Sheep (worst case scenario)

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = >29 100 µg/l	100	291 µg/l	0.00023333 µg/l	0.0000008
Daphnia sp. immobilisation	EC_{50} = >0.263 µg/l	1000	0.000263 µg/l	0.00023333 µg/l	0.89
Fish, acute toxicity	LC_{50} = 0.849 µg/l	1000	0.000849 µg/l	0.00023333 µg/l	0.27
Earthworm reproduction	NOEC = 1030 µg/kg $_{soil}$ dwt	10	103 µg/kg soil dwt	0.96 µg/kg	0.01
Dung fly larvae	EC_{50} = 1470 µg/kg dung dwt. EC_{50} = 210 µg/kg dung wwt.	100	EC_{50} = 14.7 µg/kg dung dwt. EC_{50} = 2.1 µg/kg dung wwt.	8 000 µg/kg	3810
Dung beetle larvae	LC_{50} = 3630 µg/kg dung dwt. LC_{50} = 1450 µg/kg dung wwt.	100	LC_{50} = 36.3 µg/kg dung dwt. LC_{50} = 14.5 µg/kg dung wwt.	8 000 µg/kg	552

Therefore, the following was concluded at Tier A:

Acceptable risk to groundwater.
As RQs are <1 for all scenarios except for dung organisms, an acceptable risk is indicated for all tested organisms except dung organisms.

Phase II Tier B:
As the RQ values for dung organisms are >1, further assessment of the environmental risk was required. In addition, the potential for bioaccumulation, secondary poisoning and for moxidectin to be a PBT/vPvB substance required consideration in Tier B.

Bioaccumulation and secondary poisoning:
The BCF_{SSL} (steady state BCF_{SS} normalised to a fish lipid content of 5%) ranged from 2635 (at 0.05 µg/l) to 2665 (at 0.1 µg/l). The growth corrected depuration half-life (DT_{50}) was 4.21 days at the low dose of 0.05 µg/l and 4.07 days at the high dose of 0.10 µg/l. As such, moxidectin is considered to have the potential to bioaccumulate.

The RQ value for moxidectin is below 1 for secondary poisoning for earthworm- and fish-eating predators. As such, no risk for secondary poisoning for fish- and earthworm-eating predators was determined.

PBT/vPvB:
According to the CVMP guideline on the assessment of PBT or vPvB substances in veterinary medicinal products, moxidectin can be classified as vP, B and T.

Risk to dung organisms:
Tier A and B laboratory studies demonstrated that moxidectin has potentially toxic effects on dung organisms. However, other considerations including; the suitability and attractiveness of sheep dung for feeding and/or oviposition and behavioural patterns and compensatory strategies of dung organisms may have an impact on the extent of the toxicity. It is proposed that sheep dung may be a more attractive microhabitat for dung beetles compared to dung flies.

Risk Mitigation:
Due to the risk characterisation, the following risk mitigation and environmental properties information were included on the product literature:

Other precautions regarding impact on the environment:
Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance; therefore, exposure of the environment to moxidectin must be limited to the extent possible. Treatments should be administered only when necessary and should be based on faecal egg counts or evaluation of the risk of infestation at the animal and/or herd level.

Like other macrocyclic lactones, moxidectin has the potential to adversely affect non-target organisms:

- Faeces containing moxidectin excreted onto pasture by treated animals may temporarily reduce the abundance of dung feeding organisms. Following treatment of sheep with the product, levels of moxidectin that are potentially toxic to dung fly species may be excreted over a period of 4 days and may decrease dung fly abundance during that period. It has been established in laboratory tests that moxidectin may temporarily affect dung beetle reproduction; however, studies with incurred residues indicate no long-term effects. Nevertheless, in case of repeated treatments with moxidectin (as with products of the same anthelmintic class) it is advisable not to treat animals every time on the same pasture to allow dung fauna populations to recover.
- Moxidectin is inherently toxic to aquatic organisms including fish. The product should be used only according to the label instructions. Based on the excretion profile of moxidectin when administered as the oral formulation to sheep, treated animals should not have access to watercourses during the first 3 days after treatment.

Environmental Properties:
Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance. In particular, in acute and chronic toxicity studies with algae, crustaceans and fish, moxidectin showed toxicity to these organisms, yielding the following endpoints:

Organism		**EC_{50}**	**NOEC**
Algae	*S. capricornutum*	>86.9 µg/l	86.9 µg/l
Crustaceans (Water fleas)	*Daphnia magna* (acute)	0.0302 µg/l	0.011 µg/l
	Daphnia magna (reproduction)	0.0031 µg/l	0.010 µg/l

Organism		EC_{50}	NOEC
Fish	*O. mykiss*	0.160 µg/l	Not determined
	L. macrochirus	0.620 µg/l	0.52 µg/l
	P. promelas (early life stages)	Not applicable	0.0032 µg/l
	Cyprinus carpio	0.11 µg/l	Not determined

EC_{50}: the concentration which results in 50% of the test species individuals being adversely affected, i.e. both mortality and sub-lethal effects.
NOEC: the concentration in the study at which no effects are observed.

This implies that when allowing moxidectin to enter water bodies, this may have a severe and lasting impact on aquatic life. To mitigate this risk, all precautions for use and disposal must be adhered to.

Disposal Advice:
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. Do not contaminate watercourses with the product.

III.B.2 Residues documentation

Residue Studies

This application is a generic application in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence has been accepted. Therefore, no residue depletion studies were required.

MRLs

Moxidectin is listed in Table 1 of Regulation 37/2010. The marker substance is moxidectin. MRLs have been established for edible tissues/milk, as follows:

Marker residue	Animal species	MRLs (µg/kg)	Other provisions
Moxidectin	Bovine, ovine, Equidae	Muscle: 50 µg/kg Liver: 100 µg/kg Kidney: 50 µg/kg Fat: 500 µg/kg	No Entry
	Bovine	Milk: 40 µg/kg	

Withdrawal Periods

As per the reference product:
Meat: 14 days
Milk: 5 days

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

No specific studies were required, the pharmacodynamic data is the same as for the reference product:

Moxidectin is a parasiticide active against a wide range of worm species. Its principal mode of action is interfering with neuromuscular transmission of the GABA (gamma amino butyric acid)-gated or glutamate-gated chloride channels. Moxidectin stimulates the release of GABA and increases its binding to the postsynaptic receptors. The net effect is to open the chloride channels on the postsynaptic junction to allow the inflow of chloride ions and induce an irreversible resting state. This results in flaccid paralysis and eventual death of parasites exposed to the drug.

Pharmacokinetics

Moxidectin is quickly absorbed after oral administration with peak plasma levels in less than 13 hours after dosing and is eliminated slowly with a t ½ life of approx. 7 days. The drug is distributed throughout the body tissues but due to its lipophilicity the target tissue is fat where concentrations are 10 to 20 times higher than those found in other tissues. Moxidectin undergoes limited biotransformation by hydroxylation. The only significant route of excretion is the faeces.

The applicant conducted a bioequivalence study. 40 sheep were enrolled in a single dose, GLP[3]-controlled parallel design, blinded study. Animals were not treated with moxidectin-containing product for 30 days prior to study treatment. The sheep were randomly divided into two groups of 20 and treated with either the proposed or reference product at a dose rate of 1 ml/kg. Blood samples were taken at appropriate time points. The pre-stated conditions for the demonstration of BE were met for both AUC[4] and C_{max}[5], i.e. the 90% confidence intervals (CI) for the ratio of the two treatment means were entirely contained within the limits of 80 - 125%. As such, it can be accepted that the test and reference products are bioequivalent.

[3] GLP – Good Laboratory Practice.
[4] AUC – Area under the curve.
[5] C_{max} – Maximum plasma concentration of the active substance.

Tolerance in the Target Species

Tolerance studies were not required because of the legal base of the application and because bioequivalence was established between the proposed and reference products.

Resistance

A literature review was provided. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

No data were required for this section, owing to the legal base of the application.

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 of the product is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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