IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Oxyfluke 34 mg/ml Oral Suspension for Cattle and Sheep

PRODUCT SUMMARY

EU Procedure number	IE/V/0601/001 (formerly UK/V/0617/001)
Name, strength and pharmaceutical form	Oxyfluke 34 mg/ml Oral Suspension for Cattle and Sheep
Active substances(s)	Oxyclozanide
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Date of Authorisation	26 September 2017 (IE) 26 July 2017 (UK)
Target species	Cattle,Sheep
Indication for use	For the treatment of chronic fascioliasis caused by the adult stage of *Fasciola hepatica* susceptible to Oxyclozanide.
ATCvet code	QP52AG06
Concerned Member States	Belgium, Bulgaria, Croatia, Hungary, Ireland (now RMS), Luxembourg, The Netherlands, Portugal, Slovenia, Spain. UK added via RMS change

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

This was an application for a generic product, Oxyfluke 34 mg/ml Oral Suspension for Cattle and Sheep. The reference product is Zanil Fluke Drench 34 mg/ml Oral Suspension, marketed in the UK since September 1972. The product is indicated for use in cattle and sheep for the treatment of chronic fascioliasis caused by the adult stage of *Fasciola hepatica* sensitive to oxyclozanide. Dosage is dependent on bodyweight and is provided at the rate of 10 mg oxyclozanide per kg bodyweight for cattle and 15 mg oxyclozanide per kg for sheep.
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. 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

II.A. Composition

The product contains 34 mg/ml oxyclozanide and the excipients sodium metabisulphite, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium laurilsulphate, aluminium magnesium silicate, carmellose sodium, sodium citrate and purified water.
The container/closure system consists of white, high density polyethylene backpacks (1 litre, 2.5 litre and 5 litre), closed with white polypropylene screw caps. The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the formulation and the presence of preservatives 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 series of mixing and heating and cooling processes, during which the active substance and excipients are blended.
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 oxyclozanide, an established active substance monographed in the British Pharmacopoeia, (Veterinary).
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.
All excipients are described in the European Pharmacopoeia. The container-closure system is suitably described. The product is designed for use with a standard dosing gun, for which technical drawings were provided for each component.

II.C.4. Substances of Biological Origin
A Format 3 declaration confirming that all starting materials and manufacturing processes are in compliance with the requirements of the appropriate Note for Guidance, minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) was received.

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 include those for: product appearance, oxyclozanide assay and identification, oxyclozanide-related substances, key excipient content, pH, viscosity, particle size, fill volume and microbial 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.
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 when stored under the approved conditions. Suitable stability data were available and were analysed. Data on the proposed product were acceptable with regard to all parameters investigated.

G. Other Information
Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf life after first opening the container: 6 months.
Protect from light.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation
As this was an application for a generic product, and exemption from demonstration of bioequivalence was granted under Article 7.1d) of CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2), no toxicological or pharmacological studies were required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The proposed product is directly comparable to the reference product, the only difference being some of the excipients. However, the excipients used in the proposed product are commonly used in pharmaceutical products. Other than the addition of further statements added in line with similar products, there were no changes to the user warnings and precautions as stated for the reference product:

- This product can cause irritation to skin, eyes and mucous membranes. In case of contact, rinse the affected area immediately with plenty of water.
- Contaminated clothing should be removed immediately.
- Wash hands after use.
- Wear impermeable gloves during use.
- Do not eat, drink or smoke where handling the product.
- People with known hypersensitivity to oxyclozanide or any of the excipients should avoid contact with the product.

Environmental Safety

The environmental risk assessment (ERA) was carried out in accordance with VICH[1] and CVMP[2] guidelines.

Phase I:

The Phase I VICH decision tree was completed. As the product is an endoparasiticide used in pasture animals, and the PEC_{soil} did not exceed 100 µg/ml, a Phase II ERA was required for pasture reared species only. (Questions 15 and 16 of the 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.
Results from proprietary studies and from studies available in published literature were provided. The active substance oxyclozanide was used in assays.

Physicochemical properties

Study type	**Result**	**Remarks**
Water solubility (OECD 105)	0.26 mg/l	Determined at pH7.
Dissociation constants in water pKa	-2.90 and 10.84 for amide functional group. 5.07 and 6.94 for phenol functional groups.	I-Lab 2.0, Algorithm Version: v12.1.0.50374
UV-Visible Absorption Spectrum	Principle peak 303 – 324 nm.	In publish literature
Melting Point/ Melting Range	209 – 211°C.	In publish literature
Vapour Pressure	1.0 x 10^{-6} Pa.	In publish literature
n-Octanol/Water Partition Coefficient logK_{ow} (OECD 123)	5.60 (pH 3 buffered purified water, 20°C) 5.30 (pH 5 buffered purified water, 20°C) 1.05 (pH 9 buffered purified water, 20°C) **3.53 (pH 7 buffered purified water, 20°C)**	No significant potential for bioaccumulation at pH7.

Environmental fate

Study type	**Result**	**Remarks**
Soil Adsorption (OECD 106)	Geometric mean K_{oc} = 2613	Low to slight mobility in soil
Aerobic and Anaerobic Transformation in Soil (OECD 307)	DT_{50}: 0.27 - 1.49 days (4 soils) DT_{90}: 1.15 to 248 days (4 soils)	Non-persistent in soil. Oxyclozanide displays a bi-phasic degradation, where the compound is rapidly bound to the soil and the extraction efficiency is reduced.

Environmental effects

Study type	**Endpoint and Result**
Algae, Growth Inhibition Test *Pseudokirchneriella subcapitata* (OECD 201)	72 hour EC_{50} growth rate 79 µg/l 42 hour growth NOEC 34 µg/l

Daphnia magna immobilisation (OECD 202)	48 hour EC_{50} 1.2 mg/l NOEC 0.71 mg/l
Fish, acute toxicity *Oncorynchus mykiss* (OECD 203)	96 hour LC_{50} 1.9 mg/l NOEC 1.0 mg/l
Earthworm *Eisenia foetida* (OECD 220/222)	NOEC Reproduction ≥64 mg/kg dry soil
Dung fly larvae *Musca autumnalis* (OECD 228)	EC_{50} >1000 mg/kg_{dwt} NOEC ≥1000 mg/kg_{dwt}
Dung beetle larvae *Aphodius constans* (OECD concept paper 122)	EC_{50} >1000 mg/kg_{dwt} NOEC ≥1000 mg/kg_{dwt}

There was no requirement for toxicity data related to terrestrial plants and soil organisms as the initial PEC_{soil} trigger value of 84 µg/kg was <100 µg/kg. Aquatic organisms were demonstrated to be most sensitive to oxyclozanide, with algae being the most sensitive of these.

Exposure assessment (Predicted exposure concentration)

PEC values 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 calculations correctly included use of the worst case target animal scenario of beef cattle on pasture. The following PEC values were calculated.

Outputs	**Value**	**Source**
PEC_{soil} (µg/kg)	84	CVMP Equation 2
$PEC_{groundwater}$ (µg/l)	0.45	CVMP Equation 36
Refined $PEC_{groundwater}$ (µg/l)	<0.000001	FOCUS PEARL
$PEC_{surface\ water}$ run-off drainage (µg/l)	0.15	CVMP Equation 40
$PEC_{surface\ water}$ direct excretion (µg/l)	10.45	CVMP Equation 47[1]
Refined $PEC_{surface\ water}$ direct excretion (µg/l)	0.87	CVMP Equation 50[1]
PEC_{dung}[2]	**Wet weight** 167 mg/kg (dairy cow) 254 mg/kg (beef cow) 600 mg/kg (ewe) 600 mg/kg (lamb) **Dry weight** 1282 mg/kg (dairy cow) 1952 mg/kg (beef cow) 2222 mg/kg (ewe) 2222 mg/kg (lamb)	CVMP Equation 8

1 - Only one application is considered (instead of the reasonable worst case of two treatments on pasture) as the CVMP/VICH model is concerned with a flowing stream and, as such, cumulative concentrations in water are not envisaged based upon this and the degradation profile of the compound.
2 – All target species considered as beef cattle was not the worst case.

PEC_{dung} values were determined. Appropriate information on moisture content of dung has been provided in order to convert from dung wet weight to dung dry weight.

As the $PEC_{groundwater}$ value (0.45 µg/l) derived from using the CVMP Equation 36 gave an exposure value above the trigger value of 0.1 µg/l, an unacceptable risk was concluded and further refinement using more specific groundwater modelling (FOCUS-PEARL 4.4.4) was conducted. This modelling predicted concentrations of oxaclozanide to be <0.01 µg/l in groundwater which suggests that there is no risk to groundwater from oxaclozanide.

The initial concentration in surface water, as a result of defecation and urination by cattle (direct excretion), was estimated as 10.45 µg/l (beef cattle). This estimate was further refined to 0.87 µg/l (beef cattle) based on the partitioning of the compound between water and sediment. $PEC_{sediment}$ values were not required on the basis that the RQ values for aquatic invertebrates were <1 (see below).

Risk Characterisation (Risk Quotient)

Predicted no effect concentrations (PNECs) were derived by dividing the most sensitive endpoints of the ecotoxicity data by the assessment factors (AFs), according to VICH guidelines. The PNECs were compared with the PEC values for each relevant component to determine the risk quotient (RQ), as follows:

Organism	**PEC**	**PNEC**	**RQ**
Dung fauna	2 222 000 µg/kg_{dwt}	>10 000 µg/kg_{dwt}	**222**
Earthworms	Soil 84 µg/kg	6 400 µg/kg_{dwt}	0.013
Algae	Surface water *run-off drainage* 0.15 µg/l	0.79 µg/l	0.19
Daphnia		1.2 µg/l	0.13
Fish		1.9 µg/l	0.08
Algae	Surface water *direct excretion* 10.45 µg/l	0.79 µg/l	**13.2**
Daphnia		1.2 µg/l	**8.7**
Fish		1.9 µg/l	**5.5**
Algae	Refined surface water *direct excretion* 0.87 µg/l	0.79 µg/l	**1.1**
Daphnia		1.2 µg/l	0.73
Fish		1.9 µg/l	0.46

Bold indicates unacceptable risk

As the RQ values for algae (after refinement of the surface $water_{direct\ excretion}$) and dung fauna were >1, further assessment of the environmental risk was required. Tier B refined risk characterisation assessment was performed for algae and dung fauna. Additional consideration was given to the bioaccumulation potential of oxyclozanide, as the compound acts differently (especially in terms of solubility and octanol-water partition) depending on the pH; at 'environmentally relevant' levels around pH 7 the determined log K_{OW} was below the trigger value of 4, thus no BCF study is required but at lower pH levels the trigger value is exceeded.

Following further assessment for dung fauna, the risk to dung fauna could not be excluded and, as a result, suitable safety information was added to sections 4.5.iii and 5.3 of the SPC, with equivalent data added to the product literature.

In accordance with CVMP guidance, the PNEC was refined for algae using a NOEC (34 µg/l) with an appropriate AF of 10. As a result of employing this refinement, it can be accepted that the RQ for algae is <1, indicating an acceptable risk. Furthermore, the inclusion of a 5 day exclusion period for cattle entering water can be accepted to remove any uncertainty associated with a risk to aquatic organisms and sediment dwellers from direct excretion into surface water.

Taking into consideration the fairly rapid degradation of the compound and that the value for the dissociated molecule determined around pH7 is considered to be most relevant, and pivotal for this assessment, bioaccumulation is not considered as a significant issue in this instance. Nevertheless, the potential for bioaccumulation in fish in acidic conditions is communicated in the environmental information section of the SPC and product literature.

An assessment for secondary poisoning was provided which highlighted no significant concern.

Agreed environmental safety information is as follows.

SPC Section 4.5.iii

Oxyclozanide may be toxic to dung fauna at high concentrations anticipated in dung. The possible risk to dung fauna can be reduced by avoiding too frequent and repeated use of oxyclozanide in cattle.

SPC Section 5.3

- Faeces containing oxyclozanide excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on dung degradation. Animals may be excreting oxyclozanide in dung, at levels that are potentially toxic to dung fauna, for up to 8 days post treatment.
- Oxyclozanide is toxic to dung fauna and aquatic organisms. The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of oxyclozanide in cattle. The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for 5 days after treatment.
- Oxyclozanide dissociates depending on pH. It may bioaccumulate in fish in acidic conditions.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because this was an application for a generic product. The applicant proposed the same withdrawal periods as authorised for the reference product. These have since been reviewed in light of a referral procedure under Article 35 of Directive 2001/82, as amended. The referral was relevant to all associated products.

MRLs

MRLs are listed below: Oxyclozanide as the active and marker substance:

	All ruminants
Muscle	20 µg/kg
Liver	500 µg/kg
Kidney	100 µg/kg
Fat	20 µg/kg
Milk	10 µg/kg

Withdrawal Periods

Based on the data provided, withdrawal periods cited as follows are justified:

Cattle
Meat and offal: 13 days
Milk: 108 hours (4.5 days)
Sheep
Meat and offal: 14 days
Milk: 7 days
[1] VICH – Veterinary International Conference on Harmonization.
[2] CVMP - Committee for Medicinal Products for Veterinary Use.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Pharmacodynamics

Oxyclozanide is an anthelmintic of the salicylanilide group. The active substance consists of lipophilic molecules, the chemical structure of which contains an unstable proton. The molecules are able to pass easily across cell membranes, acting as uncouplers of parasitic mitochondrial oxidative phosphorylation, causing disruption of the metabolism of the parasite. Flukicidal activity is therefore demonstrated.

Pharmacokinetics

Oxyclozanide is slowly absorbed after oral administration with peak plasma levels attained 24 hours after dosing. Excretion is predominantly faecal, with biliary excretion being the most important route of elimination (cattle studies only).

Tolerance in the Target Species

Tolerance studies were not required because of the generic basis of the application. The SPC states the following:
Section 4.6 At normal oxyclozanide dose levels, cattle may show slight softening of the faeces with the occasional animal showing increased frequency of defecation and transient inappetence.
Section 4.10 The effects of oxyclozanide over-dosage are dullness and some loosening of faeces in sheep and possible diarrhoea, inappetance and loss of weight in cattle. These effects are occasionally enhanced in animals with severe liver damage and/or dehydration at the time of dosing. At higher doses the severity of signs of toxicity increased and mortality occurred at 50 mg/kg bw and higher.

Resistance

Although specific resistance by liver fluke to oxyclozanide has not been reported in published literature, adequate warnings and precautions to preclude such an event appear in Sections 4.4 and 4.9 of the SPC. This advice includes avoiding too frequent use of the active substance, and avoidance of underdosing due to miscalculation of the weight of the animal. The use of Faecal Egg Count
Reduction Tests is advised, if appropriate, and the use of an alternative anthelmintic of another class if resistance is detected.

IV.II. Clinical Documentation

Laboratory Trials

As this was an application for a generic product, and the proposed exemption from the provision of bioequivalence was accepted, no further data were required for this section.

Field Trials

As this was an application for a generic product, and the proposed exemption from the provision of bioequivalence was accepted, no further data were required for this section.

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(s) is favourable.