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

Flukanide 30 mg/ml Oral Suspension for Sheep

Date Created: July 2023

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Flukanide 30 mg/ml Oral Suspension for Sheep, Oral suspension
Applicant	Univet Ltd, Tullyvin, Cootehill, Co. Cavan, Tullyvin, Ireland
Active substance	Rafoxanide
ATC Vetcode	QP52AG05
Target species	Sheep
Indication for use	For the treatment and control of fluke infections in sheep.

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	A generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	19/04/2023

I. SCIENTIFIC OVERVIEW

The application is for a generic product, submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference product is Ridafluke 30 mg/ml Oral Suspension, marketed by Chanelle Pharmaceuticals Manufacturing Ltd, which has been authorised in Ireland since 01 October 1998, but is not marketed in the UK.

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 Rafoxanide 30 mg/ml and the excipients Methyl Parahydroxybenzoate, Propyl Parahydroxybenzoate, Xanthan Gum, Tartrazine Yellow E10, Simethicone Emulsion, Polysorbate 20, Propylene Glycol, Colloidal Anhydrous Silica, Citric Acid Monohydrate and Purified Water.

The container consists of constructed of high-density polyethylene and the closures are screw top and constructed from polypropylene. The particulars of

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

the containers and controls performed are provided and conform to the regulation.

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 dissolving the preservatives and adding the suspending agent to form a gel. The colouring agent and the citric acid are separately dissolved, followed by the addition of the surfactant, then a percentage of the cooled gel, then the insoluble active mixed with the silica, followed part of the antifoam, the remainder of the cooled gel and then the remainder of the antifoam. After a validated mixing period the bulk suspension is filled into appropriate containers.

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 Rafoxanide an established active substance previously described in British Veterinary 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.

An active substance master file was submitted in the dossier.

Rafoxanide is packed in in a transparent low-density polyethylene (LDPE) bag. The polythene bag is manufactured from food contact LDPE granules. The primary pack is contained within a black polythene bag, also manufactured from food contact LDPE granules, within an HDPE drum. The LDPE meets EU Regulation 1935/2004 on materials and articles intended to come into contact with food. The specifications for both the primary and secondary bags include dimensional checks and identification by IR.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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, fill volume/weight, pH, active and excipients, viscosity, particle size, suspension. microbial quantity, E. coli, bacteria, yeast and mould counts,

II.F. Stability

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.

G. Other Information

Do not freeze.
Protect from light.
Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Not required due to the legal basis of the application and because bioequivalence has been established.

Toxicological Studies

Not required due to the legal basis of the application and because bioequivalence has been established.

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:,

- People with known hypersensitivity to rafoxanide or any of the listed excipients should avoid contact with the veterinary medicinal product.
- Do not eat, drink or smoke while handling the product.
- Wash hands and exposed skin before meals and after work.
- If accidental contact with the skin or eyes occurs, wash off any skin contamination with soap and water immediately. Rinse the affected eyes thoroughly with clean, fresh water. Remove any contaminated clothing immediately.

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 physico-chemical properties, environmental fate and effects. Studies were carried out using the active substance rafoxanide unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	0.0476 mg/l (pH 7, 20°C)
Dissociation constants pKa	OECD 112	5.55 (in methanol)
UV-Visible Absorption Spectrum	OECD 101	Mean Molar Absorbance (Ɛ) at 223nm= 40.718(Ɛ) Mean Molar Absorbance (Ɛ) at 285nm= 16.103(Ɛ) Mean Molar Absorbance (Ɛ) at 342nm= 7.525(Ɛ)
Melting Point	OECD 102	174.6°C
Vapour Pressure	OECD 104	High Flow Volume: <4.12 x 10^{-6} Pa (25°C) Low Flow Volume: <2.06 x 10^{-5} Pa (25°C)
n-Octanol/Water Partition Coefficient logK_{ow}	OECD 107	5.4 (pH 7, 20°C)

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	37665.82 ml/g (geometric mean)
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} of 695.4 days (arithmetic mean)

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	EC50	11.12 µg/l
Daphnia sp. immobilisation	OECD 202	EC50	3.97 µg/l
Fish, acute toxicity/ *Oncorhynchus mykiss*	OECD 203	LC50	15.8 µg/l
Earthworm, subacute/ reproduction *Eisenia fetida*	OECD 222	NOEC	124 mg/kg soil dwt
Dung fly larvae *Scathophaga stercoraria* L	OECD 228	EC50	>943.9 mg/kg dung dwt
Dung beetle larvae *Aphodius constans*	OECD draft	EC50	422.5 mg/kg dung 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)	Groundwater (µg/l)	Surface water (µg/l)	Dung mg/kg (fw)
Ewe	59.02	0.022	0.007	450 mg/kg

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.

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} 11.12 µg/l	100	0.112 µg/l	0.007	0.06
Daphnia sp. immobilisation	EC50 3.97 µg/l	1000	0.00397 µg/l		**1.76**
Fish, acute toxicity	15.8 µg/l	1000	0.0158 µg/l		0.47
Earthworm reproduction	124 mg/kg soil dwt	10	12.4 mg/kg soil dwt	59.02	0.21
Dung fly larvae*	EC_{50} 108.5 mg/kg wet dung*	100	1.1 mg/kg wet dung	450 mg/kg wet weight	**409.10**
Dung beetle larvae*	132.6 mg/kg wet dung	100	1.33 mg/kg Dry dung		**338**

*Wet weight conversion based on dung water content of 88.5
*Wet weight conversion based on dung water content of 68.8

PEC Refinement & Conclusions
As the initial PEC for groundwater is less than 0.1 µg/l, it was agreed that appropriate use of the product would not result in a risk to groundwater.

Risk quotients for terrestrial soil invertebrates, algae and fish were <1 at the initial Tier A risk characterisation. A risk to aquatic invertebrate and sediment dwelling organisms was identified; however, following refinement of the exposure assessment (PEC refinement via FOCUS and VetCalc modelling), it was demonstrated appropriate use of the product does not result in a risk to these species.

Based on the available evidence, a risk to dung fauna cannot be ruled out. Therefore, the following advice has been included on the SPC and Product Literature in order to mitigate this risk:

> *Rafoxanide is very toxic to dung insects. Long term effects on dung insects caused by continuous or repeated use cannot be excluded. Therefore, the product must only be administered once per year to affected animals only.*

The applicant has followed the CVMP guideline on the assessment of persistent, bioaccumulative and toxic (PBT) substances. The findings from this assessment confirm that rafoxanide is not a PBT substance, because it does not classify as bioaccumulative (whole fish BCF_{KLG} 774.8). In addition, the applicant has provided sufficient evidence to conclude that the product does not pose a risk of secondary poisoning to fish and earthworm eating predators.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence to the reference product was demonstrated.

MRLs

Rafoxanide is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues. The marker substance is rafoxanide.

MRLs are listed below:

	Bovine	Ovine
Muscle	30 µg/kg	100 µg/kg
Liver	10 µg/kg	150 µg/kg
Kidney	40 µg/kg	150 µg/kg
Fat / skin	30 µg/kg	250 µg/kg
Milk	Not established	Not established

Withdrawal Periods

Based on the data provided, a withdrawal period of 78 days for meat in sheep.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

There are no data requirements for this section given that the application is submitted under Article 13(1) of Directive 2001/82/EC.

The applicant has submitted one *in vivo* bioequivalence study comparing Flukanide 30 mg/ml Oral Suspension for Sheep to the reference product, Ridafluke 30 mg/ml Oral Suspension.
This was a GLP compliant study. A complete data package including study report, study protocol, pharmacokinetic methods analytical report, pharmacokinetic analysis and statistical evaluation, pharmacokinetic method validation, data capture forms and certificates of analyses were provided.

A parallel study design was chosen due to the long half-life of rafoxanide. This approach is consistent with the recommendations in the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.3-corr) and is accepted. The choice of study animals was appropriate. Animals were randomised appropriately, and blinding was satisfactory.

The assessment of bioequivalence was based upon 90% confidence limits for the ratio of the geometric means of the test and reference products for the AUC_t and C_{max} and fell within the acceptance bounds of 80 - 125%. Therefore, the test and the reference products can be claimed to be bioequivalent.

Tolerance in the Target Species

Tolerance studies were not required because the application was submitted in accordance with Directive 2001/82/EC, Article 13(1) and that the generic status of Flukanide has been confirmed, no target species tolerance data were required.

Resistance

The application was submitted in accordance with Directive 2001/82/EC, Article 13(1) and that the generic status of Flukanide has been confirmed, no resistance data were required.

IV.II. Clinical Documentation

The application was submitted in accordance with Directive 2001/82/EC, Article 13(1) and that the generic status of Flukanide has been confirmed, no clinical data were required.

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.

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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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