IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Solantel 50 mg/ml Oral Suspension for Sheep

PRODUCT SUMMARY

EU Procedure number	IE/V/0552/001 (formerly UK/V/0574/001)
Name, strength and pharmaceutical form	Solantel 50 mg/ml Oral Suspension for Sheep
Active substances(s)	Closantel
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)
Target species	Sheep
Indication for use	For the treatment of chronic and subacute fasciolosis (due to *Fasciola hepatica*). The product is effective against mature and late immature flukes (from 5 weeks immature). For the treatment of *Oestrus ovis* (Sheep Nasal Bot Fly). For the treatment of inhibited, L4 and adult stages of *Haemonchus contortus*.
ATCvet code	QP52AG09
Date of completion of the original decentralised procedure	29 June 2016 (UK) 26 August 2016 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States	Ireland (now RMS). 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 a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended). The marketing authorisation was granted on the basis that bioequivalence to the reference product was demonstrated. The reference product was Flukiver 5% w/v Oral Suspension authorised in the UK since 1986. The bioequivalence study was conducted according to the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/00 Rev.2.

The indications are for the treatment of chronic and subacute fasciolosis (due to *Fasciola hepatica*). The product is effective against mature and late immature flukes (from 5 weeks immature), the treatment of *Oestrus ovis* (Sheep Nasal Bot Fly) and the treatment of inhibited, L4 and adult stages of *Haemonchus contortus*.

The product is administered orally as a drench at a dose of 10 mg of closantel per kg bodyweight (1 ml of product per 5 kg bodyweight).

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 closantel 50 mg, as closantel sodium dihydrate 54.375 mg and the excipients propylene glycol (E1520), microcrystalline cellulose and carmellose sodium, hypromellose, sodium lauryl sulphate, simethicone emulsion and purified water.
The container/closure system consists of white high density polyethylene multidose container backpacks with high density polyethylene screw cap with induction-seal liners. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence 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 three step process; two prepared solutions are mixed together, followed by addition of the active substance and purified water.

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

II.C. Control of Starting Materials
The active substance is closantel sodium dihydrate, 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 have been provided. Appropriate CEP and ASMF[1] data were provided.

All excipients are monographed within the European Pharmacopoeia or United States Pharmacopeia. Acceptable Certificates of Analysis were provided. Packaging was suitably verified for use.

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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product include appearance, viscosity, identification and assay of closantel, pH, particle size, resuspendability, volume of fill 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. Batches were stored under

VICH[2] conditions of 30°C/65% RH and 40°C/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

G. Other Information
Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 28 days.

Do not store above 30 °C.
Keep the container in the outer carton in order to protect from light.
Store upright in the original container.

[1] ASMF – Active Substance Master File
[2] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

Warnings and precautions as listed on the product literature are in line with those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Documentation

User Safety
A user risk assessment was provided in compliance with the relevant guideline. The user safety is similar to that defined by the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The user safety warnings were brought into line with the current user safety guidelines, as follows:

- This product may be irritating to skin and eyes and users should be careful not to accidentally splash it on themselves or others.
- Wear nitrile rubber gloves when applying the product.
- In case of accidental spillage onto skin or into eyes, rinse the affected area with large amounts of clean water. If irritation persists, seek medical advice immediately and show the package leaflet or label to the physician.
- Wash hands after use.
- Do not eat, drink or smoke while handling the product.

Environmental Safety
An environmental risk assessment (ERA) was conducted in accordance with VICH and CVMP[1] guidelines.

Phase I
As the product is a parasiticide used in pasture animals, a Phase II ERA was required.

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 closantel sodium dihydrate unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	2.7 mg/l at 20°C	Bespoke study
Vapour Pressure	OECD 104	1.2×10^{-16} Pa at 25°C	Bespoke study

n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 123	$logP_{OW}$ 4.96	Bespoke study $logP_{ow}$ >4, indicates bioaccumulative potential

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 121	K_{OC} of 162 181	Non-mobile in soil, strongly binds to soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} 101.1 days (20°C) DT_{50} 191.7 days (12°C)	Closantel is classified as persistent in soil and slowly degrades in soil to multiple minor components

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test *Pseudokirchneriella subcapitata*	OECD 201	EC_{50} (72 hour)	1.00 mg/l
Daphnia magna Immobilisation	OECD 202	EC_{50} (48 hour)	36.9 µg/l
Fish, acute toxicity *Oncorynchus mykiss*	OECD 203	LC_{50} (96 hour)	25.59 µg/l
Earthworm*/Eisenia foetida* reproduction	OECD 222	NOEC	62.5 mg/kg
Dung fly larvae *Musca autumnalis*	DOTTS[1] 2004 (~OECD 228)	EC_{50}	467 mg/kg_{dwt}
Dung beetle larvae *Aphodius constans*	OECD draft	EC_{50}	1000 mg/kg_{dwt}

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 following PEC values were calculated.

Outputs	Value (Sheep)	Source
PEC_{soil} (µg/kg)	48 for ewes 36 for lambs	CVMP Equation 2
$PEC_{soil\ plateau}$ (µg/kg)	52.27 for ewes	CVMP Equation 5
PEC_{gw} (µg/l)	0.005 for ewes	CVMP Equation 32
PEC_{sw} run-off (µg/l)	0.002 for ewes	CVMP Equation 36
PEC_{dung} (mg/kg wet weight)	172.00 for ewes and lambs	CVMP Equation 8
PEC_{dung} (mg/kg dry weight)	625.5	72.5% moisture content

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} 1.04 mg/l	100	10.4 µg/l	0.002 µg/l	$1.9*10^{-4}$
Daphnia magna Immobilisation	EC_{50} 36.9 µg/l	1000	36.9 ng/l	0.002 µg/l	0.054
Fish, acute toxicity	LC_{50} 25.59 µg/l	1000	0.02559 µg/l	0.002 µg/l	0.078
Earthworm reproduction	62.5 mg/kg	10	6250 µg/kg	52.27 µg/kg	0.008
Dung fly larvae* *Musca autumnalis*	EC_{50} 467 mg/kg_{dwt}	100	4.67 mg/kg	625.5 mg/kg	134

*More conservative than the dung beetle

With the exception of dung organisms, all RQ values were <1. Based on the Tier A risk characterisation, there is low risk to soil organisms, groundwater compartment and surface water via run-off. A potential risk has been identified to dung organisms, with dung flies being the more sensitive species.

Phase II Tier B
Further assessment on the risk to dung organisms was conducted. The findings from an excretion model demonstrated a potential risk to dung fauna exists until approximately 30 days after treatment. As a result, appropriate risk mitigation and environment properties wording was required, as follows:

- Closantel is very toxic to dung fauna.

The risk to dung fauna can be reduced by avoiding too frequent and repeated use of closantel (and products of the same anthelmintic class) in sheep and lambs. Animals should not normally be treated in excess of three times a year with closantel. Closantel has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of closantel may take place over a period of several weeks. Faeces containing closantel excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.
As the estimated $\log K_{OW}$ value was >4 further assessment of the environmental risk was required. An appropriate bioaccumulation study (OECD 305) was conducted which demonstrated that correct use of the product will not result in bioaccumulation. Further, the product was demonstrated to not pose a risk of secondary poisoning in aquatic or terrestrial environments. As closantel does not classify as a bioaccumulative substance, it is not considered a PBT substance.

III.B.2 Residues documentation

Residue Studies
As bioequivalence with the reference product is demonstrated, residue depletion study data were not presented or required.

MRLs
Closantel is listed in Table 1 of Regulation (EU) 37/2010 and MRLs have been established for edible tissues and milk. The MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues
Closantel	Closantel	Ovine	1500 µg/kg	Muscle
			1500 µg/kg	Liver
			5000 µg/kg	Kidney
			2000 µg/kg	Fat
			45 µg/kg	Milk

Withdrawal Periods
Based on the data provided, the same withdrawal periods as authorised for the reference product are justified, as follows:
Meat and offal: 42 days
Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.
[1] Committee for Medicinal Products for Veterinary Use

IV. CLINICAL ASSESSMENT

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.I. Pre-Clinical Studies
In accordance with the legal basis of this application no pharmacodynamic data were required. A literature review of the pharmacodynamics of closantel was provided. The pharmacodynamics of closantel were adequately characterised. Closantel is a member of the salicylanilide class of anthelmintics. The primary action of the salicylanilides has generally been associated with the uncoupling of oxidative phosphorylation. The selective action of these anthelmintics is explained in part by the high concentrations achieved in the parasite in the absence of corresponding high tissue levels in the host.

An *in vivo* bioequivalence study was carried out according to the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/00 Rev.2. Bioequivalence was satisfactorily demonstrated. A parallel pharmacokinetic study was carried between the proposed product and Flukiver 5% w/v oral suspension. The study to determine plasma levels of closantel in sheep was carried out in compliance with GLP. The study was performed as a single parallel study involving 30 male sheep assigned to 2 groups. The test products had a single dose administered orally at a dose rate of 10mg closantel/kg bodyweight. Plasma samples were analysed using a validated fluorescence detection method. Pharmacokinetic parameters were determined using non-compartmental modelling. For both the test and reference products, the percentage of AUC_{∞} covered by the AUC_t for each individual animal was >80%, thereby indicating a reliable estimate of the extent of absorption. Peak exposure (C_{max}) is considered to be reliable as the sampling frequency around T_{max} was sufficient. The study demonstrated that the test and reference products were statistically bioequivalent with regard to C_{max} and AUC_t.

Resistance

The bibliographic information provided suggests that no reports of resistance were found in the EU.
Adequate precautions appear on the product literature.

IV.II. Clinical Documentation

Clinical studies were not required as bioequivalence was demonstrated with the reference product via a suitable *in vivo* bioequivalence study.

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.