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

Flydown 10 mg/ml Pour-on Solution for Cattle and Sheep

Date Created: November 2024

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Flydown 10 mg/ml Pour-on Solution for Cattle and Sheep
Applicant	VIRBAC, 1ère avenue 2065m LID, 06516 Carros , France
Active substance	Deltamethrin
ATC Vetcode	QP53AC11
Target species	Cattle Sheep
Indication for use	As a topical application for the treatment and prevention of infestations by lice and flies on cattle; ticks, lice, keds and established blowfly strike on sheep and lice and ticks on lambs. On cattle: For the treatment and prevention of infestations by both sucking and biting lice, including *Bovicola bovis*, *Solenopotes capillatus*, *Linognathus vituli* and *Haematopinus eurysternus*. Also as an aid in the treatment and prevention of infestations by both biting and nuisance flies including *Haematobia irritans*, *Stomoxys calcitrans*, *Musca* species and *Hydrotaea irritans*. On sheep: For the treatment and prevention of infestations by ticks *Ixodes ricinus* and by lice (*Linognathus ovillus, Bovicola ovis*), keds (*Melophagus ovinus*). For the treatment of established blowfly strike (usually *Lucilia spp*). On lambs: For the treatment and prevention of infestations by ticks *Ixodes ricinus* and by lice *Bovicola ovis*.

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 hybrid application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10a) as amended.
Date of conclusion of the procedure	22/08/24

I. SCIENTIFIC OVERVIEW

This is a generic hybrid application as new data has been included to establish a withdrawal period for sheep milk. The reference product is Fly & Lice Spot on Insecticide 1% w/v Cutaneous Solution which has been authorised in the UK since 1984.

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 deltamethrin and the excipients triglycerides medium chain.

The container/closure system consists of HDPE bottles. 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.

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

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.

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

II.C. Control of Starting Materials

The active substance is deltamethrin, an established active substance described in the 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.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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 suitable for this pharmaceutical form.

II.F. Stability

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

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 5 years
Shelf-life after first opening the immediate packaging: 1 year
Store in tightly closed original container away from food, drink and animal feeding stuffs.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that deltamethrin is a synthetic pyrethroid possessing insecticidal and acaricidal activity. It is one of a large family of pyrethroid esters which have evolved as synthetic analogues of the original insecticidal extracts isolated from powdered pyrethrum flowers. Deltamethrin is an alpha- cyano pyrethroid and is a member of the second generation of pyrethroids in which the overall stability of the molecule is improved with correspondingly increased resistance to photo- and bio-degradation and enhanced insecticidal activity. It is more potently toxic to insects and acarines because of the slower rate of metabolism.
The precise mode of insecticidal activity of pyrethroids remains uncertain, but they are potent neurotoxins in insects, causing failure in sensory coordination and disorganised motor activity, hence the 'knock-down' effect. Pyrethroids are metabolised through oxidative and neurotoxic pathways far more rapidly in mammals, so that neurotoxic effects can only occur at dosages which are many orders of magnitude greater than those required for ectoparasitic activity.
Two physiological mechanisms are likely to contribute to deltamethrin-resistance: mutation of the molecular deltamethrin target or through metabolic enzyme glutathione-S-transferases.

After dermal application, deltamethrin is slightly absorbed through skin of cattle and sheep.
Pyrethroids are metabolised through oxidative and neurotoxic pathways.
The main route of excretion of the absorbed amount in the target animal is the faeces.

Bioequivalence has been established with the reference product.

Toxicological Studies

Not required due to the legal basis of the application.

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:

- Deltamethrin can cause hypersensitivity (allergic) reactions. People with known hypersensitivity to deltamethrin should avoid contact with the product.
- Wear protective clothing including waterproof apron and boots and impervious gloves when either applying the product or handling recently treated animals.
- Remove heavily contaminated clothing immediately and wash before re-use.
- Wash splashes from skin immediately with soap and plenty of water.
- Wash hands and exposed skin after handling this product and before meals.
- In case of contact with eyes, rinse immediately with plenty of clean, running water and seek medical advice.
- In case of accidental ingestion, wash out mouth immediately with plenty of water, seek medical advice and show the package leaflet to the physician.
- Do not smoke, drink or eat while handling the product.
- This product contains deltamethrin which may produce tingling, itchiness and blotchy redness on exposed skin. If you feel unwell after working with this product, seek medical advice immediately and show the package leaflet or the label to the physician.

Environmental Safety

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

Phase I:
The initial predicted environmental concentration (PEC) in soil is less than 100 µg/kg for all species; however, as the product is a parasiticide, a Phase II was required for sheep and cattle raised on pasture (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 deltamethrin unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	2 µg/l
Dissociation constants in water pKa	OECD 112	n/a. Study abandoned due to low water solubility.
UV-Visible Absorption Spectrum	OECD 101	210 nm
Melting Point/Melting Range	OECD 102	99 - 100°C
Vapour Pressure	OECD 104	≤3.93 x 10^{-7} Pa
n-Octanol/Water Partition Coefficient	OECD 117	logP_{ow} >5.1

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 121	K_{oc} = >15 848.932 l/kg
Aerobic and Anaerobic Transformation in Soil	None	DT_{50} = 72 days

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/ *Scenedesmus subspicatus*	OECD 201	EC50	>1.47 µg/l
Daphnia sp. Immobilisation	OECD 202	EC50	0.025 µg/l
Fish, acute toxicity/ *Oncorhynchus mykiss*	OECD 203	LC50	0.8 µg/l
Soil Micro organisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	n/a
Terrestrial Plants, Growth Test/*Species*	OECD 208	EC50	n/a
Earthworm*/ Eisenia fetida* subacute/reproduction	OECD 222	NOEC	22.61 mg/kg
Dung fly larvae	None	EC50	110 µg/kg
Dung beetle (adult)	None	EC50	10 µg/kg

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)	Surfacewater (µg/l)
Dairy cow	0.468	0.00042	0.00014
Beef cattle	1.267	0.00113	0.00038
Lamb	1.667	0.0015	0.0005
Sheep	1.000	0.00089	0.00030

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.

Dairy cow

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = >1.47 µg/l	100	0.0147 µg/l	0.00014 µg/l 0.117 µg/l (direct excretion)	0.009 7.95 (direct excretion
Daphnia sp. immobilisation	EC_{50} = 0.025 µg/l	1000	0.000025 µg/l	0.00014 µg/l 0.117 µg/l (direct excretion)	5.6 4680 (direct excretion)
Fish, acute toxicity	EC_{50} = 0.8 µg/l	100	0.008 µg/l	0.00014 µg/l 0.117 µg/l (direct excretion)	0.0175 14.62 (direct excretion)
Soil Micro organisms:	n/a	n/a	n/a	n/a	n/a
Terrestrial Plants, Growth	n/a	n/a	n/a	n/a	n/a
Earthworm reproduction	NOEC = 22.61 mg/kg	10	2261 µg/kg	0.486 µg/kg	0.00021
Dung fly larvae	LC_{50} = 110 µg/kg	100	1.1 µg/kg	2780 µg/kg	2527
Dung beetle adult	LC_{50} = 10 µg/kg	1000	0.01 µg/kg	2780 µg/kg	278000

Beef cattle

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = >1.47 µg/l	100	0.0147 µg/l	0.00038 µg/l 0.317 µg/l (direct excretion)	0.025 21.56 (direct excretion
Daphnia sp. immobilisation	EC_{50} = 0.025 µg/l	1000	0.000025 µg/l	0.00038 µg/l 0.317 µg/l (direct excretion)	15.2 12680 (direct excretion)
Fish, acute toxicity	EC_{50} = 0.8 µg/l	100	0.008 µg/l	0.00038 µg/l 0.317 µg/l (direct excretion)	0.0475 39.62 (direct excretion)
Soil Micro organisms:	n/a	n/a	n/a	n/a	n/a
Terrestrial Plants, Growth	n/a	n/a	n/a	n/a	n/a
Earthworm reproduction	NOEC = 22.61 mg/kg	10	2261 µg/kg	1.267 µg/kg	0.00056
Dung fly larvae	LC_{50} = 110 µg/kg	100	1.1 µg/kg	7690 µg/kg	6991
Dung beetle adult	LC_{50} = 10 µg/kg	1000	0.01 µg/kg	7690 µg/kg	7690000

Lamb

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = >1.47 µg/l	100	0.0147 µg/l	0.0005 µg/l	0.034
Daphnia sp. immobilisation	EC_{50} = 0.025 µg/l	1000	0.000025 µg/l	0.0005 µg/l	20
Fish, acute toxicity	EC_{50} = 0.8 µg/l	100	0.008 µg/l	0.0005 µg/l	0.0625
Soil Micro organisms:	n/a	n/a	n/a	n/a	n/a
Terrestrial Plants, Growth	n/a	n/a	n/a	n/a	n/a
Earthworm reproduction	NOEC = 22.61 mg/kg	10	2261 µg/kg	1.667 µg/kg	0.00074

Test organism	End point	AF	PNEC	PEC	RQ
Dung fly larvae	LC_{50} = 110 µg/kg	100	1.1 µg/kg	55 560 µg/kg	50 509
Dung beetle adult	LC_{50} = 10 µg/kg	1000	0.01 µg/kg	55 560 µg/kg	55.56 x 10^6

Sheep

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} = >1.47 µg/l	100	0.0147 µg/l	0.0003 µg/l 0.00014 (direct excretion)	0.020 0.009 (direct excretion)
Daphnia sp. immobilisation	EC_{50} = 0.025 µg/l	1000	0.000025 µg/l	0.0003 µg/l 0.00014 (direct excretion)	12 5.6 (direct excretion)
Fish, acute toxicity	EC_{50} = 0.8 µg/l	100	0.008 µg/l	0.0003 µg/l 0.00014 (direct excretion)	0.0375 0.175 (direct excretion)
Soil Micro organisms:	n/a	n/a	n/a	n/a	n/a
Terrestrial Plants, Growth	n/a	n/a	n/a	n/a	n/a
Earthworm reproduction	NOEC = 22.61 mg/kg	10	2261 µg/kg	1.000 µg/kg	0.00044
Dung fly larvae	LC_{50} = 110 µg/kg	100	1.1 µg/kg	25 000 µg/kg	27 727
Dung beetle adult	LC_{50} = 10 µg/kg	1000	0.01 µg/kg	25 000 µg/kg	25 x 10^6

As all RQ values were <1 for earthworms, assessment for this species concluded at Tier A. Assessment also concluded in Tier A for groundwater as PECs were below the trigger value of 0.1 µg/l. RQ values >1 were calculated for algae and fish (dairy cows and beef cattle via direct excretion) *daphnia* (all target species, surface water and via direct excretion), dung fly larvae and dung beetles (all target species); consequently, further assessment of environmental risks to these species were required in Tier B.

PEC values were refined based on pharmacokinetic data, whereby 7.5% of the absorbed dose is excreted from treated animals. Based on this refinement,

acceptable risks (RQ <1) were determined for aquatic species for surface water, however, risks were still identified for dung fauna and *daphnia* via direct excretion to surface water. No further refinement of the risks to dung fauna were possible; however, appropriate risk mitigation measures were proposed and assessment concluded in Tier B.

Following further refinement via partitioning to sediment, unacceptable risks were still identified for *daphnia* via direct excretion to surface water; however, when based on daily excretion, RQ levels were found to be acceptable (<1) and assessment concluded in Tier B. No unacceptable risks to sediment environments were identified. The product is not expected to pose an unacceptable risk to the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

A residue depletion study in milk from ewes was conducted in order to establish a withdrawal period of zero hours.

No other residue depletion studies were conducted because of the legal basis of the application.

MRLs

Deltamethrin is included in the GB MRL list with a 'No MRL required' status.

Withdrawal Periods

Based on the data provided, a withdrawal period of 17 days for meat in cattle and 35 days for meat in sheep and 0 hours for both species for milk are justified.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Bioequivalence was established therefore no studies were required.

Tolerance in the Target Species

Tolerance studies were not required due to the legal basis of the application.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Not required due to the legal basis 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.

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