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

Dectospot 10 mg/ml Spot-on Solution for Cattle and Sheep
Ectron 10 mg/ml Spot-on Solution for Cattle and Sheep

Date Created: June 2015

Updated: May 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Dectospot 10 mg/ml Spot-on Solution for Cattle and Sheep Ectron 10 mg/ml Spot-on Solution for Cattle and Sheep
Applicant	Bimeda Animal Health Limited 2,3,4 Airton Close Tallaght Dublin Ireland D24 E032
Active substance	Deltamethrin
ATC Vetcode	QP53AC11
Target species	Cattle and sheep
Indication for use	As a topical application for the control of lice and flies on cattle; ticks, lice, keds and established blowfly strike on sheep and lice and ticks on lambs. On cattle**:** for the control of both sucking and biting lice, including *Damalinia bovis, Solenopotes capillatus, Linognathus vituli* and *Haematopinus eurysternus* on all ages of cattle including dairy cattle producing milk for human consumption. Also as an aid in the control of both biting and nuisance flies including *Haematobia irritans*, *Stomoxys calcitrans, Musca* species and *Hydrotaea irritans.* On sheep: For the control of ticks *Ixodes ricinus* and of lice and keds and established blowfly strike. On lambs: For the control of ticks *Ixodes ricinus* and 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.

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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.

I. SCIENTIFIC OVERVIEW

These were applications for generic products in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference product is Zoetis Spot On Inseciticide 1% w/v Cutaneous Solution. The indication is for the control of lice and flies on cattle, lice, tick, keds and blowfly strike on sheep and lice and ticks on lambs. The product is administered at 10 mg/ml, with a 10 ml dose provided to cattle, a 5 ml dose for sheep and a 2.5 ml dose for lambs under 10 kg or at one month of age. A biowaiver in accordance with *EMA/CVMP/016/00-Rev.2, 7.1 (d)* was permitted for this product, and as such, bioequivalence studies were not required to be submitted.

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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 10 mg/ml deltamethrin and the excipients are triglycerides, medium chain.

The container/closure system consists of:

a) 250 ml and 500 ml natural high-density polyethylene bottle with internal graduated calibration chamber with a black plastic heat-sealed screw cap.

b) Carton containing one1 litre or one or two 2.5 litre white high density polyethylene flexipack with white polypropylene closures and induction heat-sealed screw-cap and spouted cap for connection to applicator.

Not all pack sizes may be marketed.

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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The manufacturing process is one of simple mixing to homogenisation of the components and subsequent filling into containers.

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. Suitable data were provided in an Active Substance Master File. The excipients conform to the relevant European Pharmacopoeial monograph. Suitable specification data were provided for the containers.

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. A relevant Format 3 declaration was provided.

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. Tests include those for appearance, colour, density, water content, extractable volume, active substance identification, impurities 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. Suitable data were submitted to support a re-test period for the active substance for 2 years, and for a stability period of 2 years for the finished product.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf-life after first opening the immediate packaging: 3 months

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13 (1), and bioequivalence with a reference product was accepted, pharmacological and toxicological data were 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

The user safety is the same as 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.

Environmental Safety

An Environmental Risk Assessment (ERA) was conducted in accordance with VICH and CVMP guidelines.

Phase I:
As the product is an ectoparasiticide for use in species reared on pasture, a Phase II assessment was required (as stipulated in 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.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	0.0907 mg/l	Published source
Dissociation constants in water pKa	OECD 112	N/A	N/A
Melting Point/Melting Range	OECD 102	99 - 102	Published source
Vapour Pressure	OECD 104	1.2×10^{-7}	Published source
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 123	>6.21	$logP_{OW}$ >4, indicates potential for bioaccumulation

Metabolism and Excretion
Data showed that deltamethrin is excreted in faeces following dermal application and that little deltamethrin is excreted in urine. In accordance with the MRL summary report for deltamethrin (EMEA/MRL/530/98 FINAL, April 1999), as a worst case it could be assumed that if 72% remains at the site of application, 28% is absorbed then excreted and this was taken in to consideration when refining the predicted environmental concentration in surface water from direct excretion.

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 121	>200 000 K_{oc}	Non-mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} = 72 days Equating to 154 days when normalised to a temperature of 12°C (required for PBT assessment)	DT_{90} <1 year

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test (*Pseudokirchneriella subcapitata*)	OECD 201	EC_{50}[3]	>3.69 µg/l
Daphnia magna immobilisation reproduction	OECD 202 OECD 222	EC_{50} NOEC[4] EC_{50} NOEC	0.0753 µg/l 0.0252 µg/l 0.0079 µg/l 0.0051 µg/l
Sediment invertebrate *(Chironumus riparius)*	OECD 218	LC_{50}	>166 µg/kg
Fish, acute toxicity in rainbow trout (*Oncorhynchus mykiss)* bluegill sunfish *(Lepomis macrochirus)*	OECD 203	 LC_{50}[5] LC_{50}	 0.688 µg/l 0.727 µg/l
Earthworm (*Eisenia foetida)* sub-acute/reproduction	OECD 220/222	EC_{10}[6]	12200 µg/kg
Dung fly larvae (*Scathophaga stercoraria)*	OECD 228	LC_{50}	32 µg/kg
Dung beetle larvae (*Aphodius constans*)	OECD 122	LC_{50}	8 µg/kg

PEC values for soil, dung, groundwater, surface water and sediment were calculated in accordance with the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. Refinement was carried out as necessary and the following PEC values were calculated.

[3] EC_{50} – concentration that will have an effect on 50% of the population of test organisms
[4] NOEC – no observable effect concentration
[5] LC_{50} – concentration that kills half a sample population
[6] EC_{10} – concentration that will have an effect on 10% of the population of test organisms

Target animal	PEC					
	Soil	Dung	Groundwater	Surface water, run-off	Surface water, direct excretion	Sediment
	(µg/kg)		µg/l			$µg/kg_{dwt}$
Dairy Cow	1.43	500			0.000068**	0.26
Beef Cattle	3.76					
Sheep	3.02	N/A			0.000002**	21.68
Lambs	5.00*		0.000119	0.000040		0.0042

*Initial PEC_{soil} used to calculate groundwater and surface water PECs
**$PEC_{swdirectexcretion}$ refined

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.

Cattle and Sheep

Test organism	End point (µg/kg or l)	AF	PNEC (µg/kg or l)	PEC (µg/kg or l)	RQ
Algae, Growth Inhibition	EC_{50}= >3.69	100	0.0369	0.000040	<0.01
Daphnia sp. immobilisation	EC_{50} = 0.0753	1000	0.0000753	0.000040	0.53
Fish, acute toxicity	LC_{50} = 0.688	1000	0.000688	0.000040	0.06
Earthworm reproduction	EC_{10} = 12200	10	1220	5.0	<0.01
Dung fly larvae	LC_{50} = 32	100	0.32	500	1563
Dung beetle larvae	LC_{50} = 8	100	0.08	500	6250

Tier B

From the provided OECD 305 bioaccumulation study, deltamethrin was shown to have a BCF value less than 2000. Therefore, deltamethrin cannot be considered a PBT substance.

As the preliminary RQ[7] value for aquatic invertebrates and dung insects was >1, further assessment was required. In summary, a high risk to dung insects was identified which could persist for a period of time after treatment. The risk could not be further refined so appropriate risk mitigate measures were proposed (see below). In order to prevent a risk to sediment-dwelling organisms, sheep should be prevented from crossing water courses within one hour of treatment with the product. As a result, the following risk mitigation measures pertaining to dung organisms and aquatic invertebrates were included on the SPC and product literature.

[7] RQ – Risk Quotient = PEC/PNEC

- Deltamethrin is very toxic to dung fauna, aquatic organisms and honey bees, is persistent in soils and may accumulate in sediments.
- The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of deltamethrin (and other synthetic pyrethroids) in cattle and sheep, e.g. by using only a single treatment per year on the same pasture.
- The risk to aquatic ecosystems will be further reduced by keeping treated sheep away from water bodies for one hour immediately after treatment.

In addition, the following environmental information was required.

- Deltamethrin has the potential to adversely affect non-target organisms, both in water and in dung. Following treatment, excretion of potentially toxic levels of deltamethrin may take place over a period of 4 weeks. Faeces containing deltamethrin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.
- Deltamethrin is very toxic to dung fauna, aquatic organisms and honey bees, is persistent in soils and may accumulate in sediments.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the products are formulated to be essentially similar to the reference product.

MRLs

MRLs are listed below for deltamethrin:

Tissue source	**All ruminants: MRL (µg/kg)**
Muscle	10
Liver	10
Kidney	10
Fat	50
Milk	20

The only excipient, 'Triglycerides, medium chain (trade name Miglyol 812)' is considered to be in Table I of Regulation 37/2010, with 'no MRL required' status, under the entry for 'Fractionated Coconut Oil'.

Withdrawal Periods

Based on the data provided, withdrawal periods were stipulated as follows:

Cattle (meat) – 17 days
Cattle (milk) – zero hours
Sheep (meat) – 35 days

This product is not authorised for use in ewes producing milk for human consumption.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been established, efficacy studies are not required. A biowaiver, which allows *in vitro* data to be accepted for an application in lieu of *in vivo* bioequivalence data, was permitted in accordance with EMA/CVMP/016/00-Rev.2, 7.1 (d).

IV.I. Pre-Clinical Studies

No further data were required.

IV.II. Clinical Documentation

No further 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(s) is favourable

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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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