College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ectofly 12.5 mg/ml Pour-on Solution for Sheep

Date Created: February 2015 (UK)

Updated: December 2019 (NL)

RMS transfer from UK to NL in 2018: application number changed from UK/V/0498/001 to NL/V/0255/001

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0255/001
Name, strength and pharmaceutical form	Ectofly 12.5 mg/ml Pour-on Solution for Sheep
Applicant	Bimeda Animal Health Ltd. Unit 2/3/4 Airton Close, Tallaght, Dublin 24 Ireland
Active substance(s)	Cypermethrin tech. (cis:trans 80:20)
ATC Vetcode	QP53AC08
Target species	Sheep
Indication for use	For the treatment and control of headflies. For the treatment of tick infestation with a persistent efficacy of 10 weeks (the majority of ticks killed within 3 hours) and treatment of biting lice in sheep. For the prevention and treatment of blowfly strike in sheep.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (http://www.HMA.eu)

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.
Date of completion of the original decentralised procedure	24th September 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	France, Germany, The Netherlands, Portugal

I. SCIENTIFIC OVERVIEW

This application for a generic product, Fly Off 12.5 mg/ml Pour-on Solution for Sheep, was submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Young's Vector, first authorised in the UK in 1996. The proposed product is 'essentially similar' to the reference product. The proposed product is indicated for the treatment and control of headflies in sheep, for the treatment of tick infestation with a persistent efficacy of 10 weeks, and for the treatment of biting lice. The product is also indicated for the prevention and treatment of blowfly strike.

The product is administered by means of an applicator gun, which is supplied with different nozzles for correct administration, according to the relevant indication. Dosage varies depending on the weight of the sheep and the type of indication. The SPC[1] carries the detailed information.

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 [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 CONSTIUENTS

II.A. Composition

The product contains 12.5 mg/ml cypermethrin tech. (cis:trans /80:20), and the excipients Green S Dye (E142) and diethylene glycol monobutyl ether.

The container/closure system consists of white high-density polyethylene Carrick flat bottom containers with polypropylene closures and induction heat-sealed wadding, at 1 litre, 2.5 litre and 5 litre pack sizes. 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 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 a simple solubilisation process, with active substance and excipients being mixed as appropriate. In-process analyses are performed at various time points, before the product is filled into containers.

II.C. Control of Starting Materials

The active substance is cypermethrin, an established active substance not described in a pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice (GMP), in accordance with an active substance master file. An appropriate specification was supplied by the applicant. 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.

The excipients are not monographed in a pharmacopoeia. Suitable specifications were provided for both excipients. Suitable data were provided which demonstrated the appropriateness of containers for the active substance and finished product.

II.C.4. Substances of Biological Origin

A UK Format 3 statement declared that 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. Tests include those for appearance, identification, colour, active substance content, impurities, water content, specific gravity fill volume and packaging appearance.

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 tests on the active substance included those for stress stability, photostability, long term stability and accelerated stability.

Stress Stability

Data showed that little or no degradation occurred under conditions of high temperature (100^{o}C), oxidation, or hydrolysis at pH 1.0, 7.0 and 9.0.

Photostability

Data showed that the active substance was sensitive to light when exposed to direct artificial light, but not when stored in appropriate commercial packaging.

Long Term Stability

Three commercial batches of cypermethrin were stored at 30^{o}C/65% RH for 30 months. No adverse effects were noted.

Accelerated Stability

Six months of data for the active substance stored at 40^{o}C/75% RH were submitted, and no degradation of cypermethrin was observed. A retest period of 2 years for the active substance was supported.

For the finished product, suitable data were received from 3 pilot batches, produced on a commercial scale, and stored under VICH[3] conditions, (25^{o}C/60% RH, 40^{o}C/75% RH. From the 12 months data available for the finished product at

[3] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

40°C/75% RH, and 24 months data available at 25°C/60% RH, it was seen that no significant degradation occurred. In-use product data were also considered acceptable.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

Shelf life after first opening of the immediate packaging: 3 months.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (3), and essential similarity with a reference product has been established, results of pharmacological and toxicological tests are not required. Warnings and precautions as listed on the product literature are the same as 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 suitable user risk assessment (URA) was provided in compliance with the relevant guideline. The warnings for the proposed product are the same as those of the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- This product is harmful if swallowed and may cause skin, eye or respiratory irritation. This product may also cause hypersensitivity reactions.
- Avoid skin and/or eye contact.
- Avoid children from getting access to the product or treated animals.
- Use in a well-ventilated area and avoid inhaling the vapour.
- Wear eye protection, protective clothing, rubber gloves and boots when applying the product and handling the animal until the product has dried.
- Wear a disposable face-mask when applying as a fan-spray for the prevention of blowfly-strike.
- Make sure when attaching the recommended applicator gun onto the container that the coiled retainer is secured onto the cap and the applicator.

- Wash splashes from skin and eyes immediately with plenty of clean water. If irritation persists seek medical advice immediately and show the package leaflet to the physician.
- Remove contaminated clothing immediately and wash exposed skin with plenty of clean water.
- Do not eat, drink or smoke whilst using the product. Wash hands immediately after use.
- In case of accidental ingestion or mouth contact, immediately rinse the mouth with plenty of water and seek medical advice.

Environmental Safety

The environmental risk assessment (ERA) was carried out in accordance with VICH (CVMP/VICH/529/98 and CVMP/VICH/790/03) and CVMP (EMEA/CVMP/ERA/418282/2005 – Rev) guidelines.

Phase I:
The product is a cutaneous pour-on solution for use in sheep. As a result of the use of the product, cypermethrin has the potential to be released into the environment through excretion by animals raised on pasture. A Phase II ERA was required as the product is a parasiticide used in pasture animals (Question 16 of the Phase I decision tree).

Phase II:
A Tier A Phase II 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 cypermethrin (Cis:Trans 80:20, respectively) unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	4.00 µg/l at pH7	Published source
Melting Point	OECD 102	61 – 83^{o}C	Published source
Vapour Pressure	OECD 104	2.0 x 10^{-4} mPa	Published source
n-Octanol/Water Partition Coefficient	OECD 107	6.6 at pH 7	logP_{OW} >4, indicates potential for bioaccumulation

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption (7 data sets)	Broadly in accordance with OECD 106	K_{oc} = 40495 l/kg	Non-mobile in soil.
Aerobic and Anaerobic Transformation in sandy loam (14% clay 2.3% organic matter)	Broadly in accordance with OECD 307	DT_{50} = 190 days at 12ºC	Indicates that cypermethrin is persistent in soil

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test with *Pseudokirchneriella subcapitata*	OECD 201	ErC_{50}[4] 72 h NOEC[5] 72 h	>7.57 µg/l
Daphnia sp. *Daphnia magna* acute and chronic tests	US EPA guidelines broadly in accordance with OECD 202	NOEC 48 h	0.025 µg/l
Sediment invertebrate in *Chironumus tentans*	US EPA guidelines broadly in accordance with OECD 218 & 219	NOEC	3.8 µg/kg dry weight
Fish, acute toxicity in *Poecilia reticulata*	Broadly in accordance with OECD 203	LC_{50}[6] 96 h	9.43 µg/l
Earthworm/*Species* sub-acute/reproduction	OECD 220/222	NOEC	5000 µg/kg dry weight
Dung fly larvae	Broadly in accordance with OECD 228	LC_{50}	0.45 mg/kg dry weight
Dung beetle larvae	OECD draft	LC_{50}	0.21 mg/kg dry weight

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. Treatment of lambs was considered as worst case. 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 to determine the risk quotient (RQ), as follows.

Test organism	End point (µg/kg or l)	AF	PNEC (µg/kg or l)	PEC (µg/kg or l)	RQ
Earthworm reproduction	NOEC = 5000	10	500	21	0.04
Dung fly larvae	LC_{50} = 45	100	0.45	240	533
Dung beetle larvae	LC_{50} = 21	100	0.21	240	1143

The RQ values for dung insects are so high that it is unlikely that further studies will reduce the value to <1.

The $PEC_{groundwater}$ value for cypermethrin was estimated as 0.007 µg/l. As the concentration is <0.1 µl no further assessment was required.

[4] EC_{50} – Half the maximal effective concentration
[5] NOEC – No observable effect concentration
[6] LC_{50} – The concentration that kills half a sample population

The $PEC_{surface\ water\text{-}initial\text{-}run\text{-}off}$ for cypermethrin was estimated as 0.0023 µg/l

End point	Result	AF	PNEC
Daphnia magna	48 h NOEC 0.025 µg/l	1000	0.000025 µg/l
Fish	96 h LC_{50} 9.43 µg/l*	1000	0.00943 µg/l
Algae	72 h EC_{50} >7.57 µg/l	100	0.076 µg/l

End point	PEC	PNEC	RQ
Daphnia magna	$PEC_{surfacewater}$ (run off) 0.0023 µg/l	0.000025 µg/l	**92**
Fish		0.031 µg/l	0.07
Algae		0.076 µg/l	0.03

* when the Log P_{ow} is >5 then the RQ value should be <0.1

As the RQ value (92) for daphnids exceeded the regulatory trigger, further refinement of the soil PEC was undertaken. The worst case $PEC_{soil\text{-}initial}$ was refined by a factor of 54% (from excretion study), resulting in a $PEC_{soil\text{-}refined\_excretion}$ of 0.0013 µg/l; the resultant RQ value still exceeded the regulatory trigger (50) and further refinement was performed using the FOCUS modelling (PRZM, MACRO and TOXSWA). The resulting RQ values for daphnids were less than the regulatory trigger for 11 out of 14 scenarios selected (RQ < 0.4); in the remaining three scenarios, all of which were streams, the risk quotient exceeded the regulatory trigger (< 6). In accordance with CVMP guidance states that time-weighted average (TWA) concentrations corresponding to the exposure period should be used for risk assessment purposes. Using the 7 day TWA values were compared with the PNEC and the resultant RQ values remained to be higher than the regulatory trigger. This risk has been addressed in the SPC by the inclusion of appropriate risk mitigation measures (see below).

A Tier B assessment was performed, which consisted of a review of literature describing the toxicity of cypermethrin on cattle dung. These data were considered acceptable for inclusion into the environmental risk assessment report. The data showed that use of cypermethrin has a detrimental effect on flies and larvae for 7-14 days, and on beetles for up to 3 days. Use of the product should be restricted to one dose per season, which limits the effects on the environment. 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 addition, as a logPow of greater than 4 was determined the potential for cypermethrin to bioaccumulate was addressed as well as an assessment of the potential for cypermethrin to be a persistent (P), bioaccumulative (B) and toxic (T) substance. From the provided OECD 305 bioaccumulation study, cypermethrin was shown to have a BCF value less than 2000. Therefore, as cypermethrin is considered to be persistent (P) and toxic (T) but not bioaccumulative (B), it is not classified as PBT, nor vPvB. However, in light of there being opposing evidence on whether cypermethrin has a BCF >2000 l/kg, additional environmental information pertaining to the potential PBT properties of the cypermethrin was required (see below).

The following risk mitigation measures pertaining to dung organisms and aquatic invertebrates were included on the SPC and product literature.

- Cypermethrin is extremely toxic to aquatic and dung organisms. As a precautionary measure sheep must be kept away from watercourses for at least 12 hours following treatment.
- Long term effects on dung insects caused by continuous or repeated use of pyrethroid ectoparasiticides cannot be excluded.
- Given the risks to the environment the use of the product should be limited to one treatment per year per pasture.

In addition, the following environmental information pertaining to the potential PBT properties of the cypermethrin was required.

- Cypermethrin is persistent, toxic and may have the potential to bioaccumulate, Cypermethrin is thus possibly a PBT compound. Cypermethrin has been taken up on the list of 'priority substances' (Directive 2013/39/EU), which means that its presence in water bodies is monitored regularly.

III.B.2 Residues documentation

Because the product was established as being identical to the reference product, no additional data were required.

Withdrawal Periods

Based on the data provided, a withdrawal period of 8 days for meat and offal was agreed. The product is not to be administered to animals producing milk for human consumption, including non-lactating ewes in the dry period.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (3), and essential similarity with a reference product has been established, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. An additional warning was added to the SPC in light of sheep deaths due to overdose in association with use of the reference product:

- To ensure administration of a correct dose, body weight should be determined as accurately as possible; accuracy of the dosing device should be checked.

IV.I. Pre-Clinical Studies

As this is a generic application according to Article 13 (3), and essential similarity with a reference product has been established, pre-clinical studies are not required.

IV.II. Clinical Documentation

As this is a generic application according to Article 13 (3), and essential similarity with a reference product has been established, clinical studies are not 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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

Summary of change	**Section updated**	**Approval date**
Change in the QPPV contact details and/or back-up procedure (UK/V/xxxx/IA/083/G)	N/A	5 May 2015
Introduction of a new Pharmacovigilance system (Cross Vetpharm Group Ltd. DDPS) which has been assessed by the relevant national competent authority/EMA for another product of the same MAH (UK/V/0498/001/IB/002)	N/A	14 September 2017
MAH transfer from Zoetis B.V. to Cross Vetpharm Group Ltd. (National variations)	Module 1	November 2017
Change in the specification parameters and/or limits of an excipient Change in test procedure for the finished product Change in the specification parameters and/or limits of the immediate packaging of the finished product Change in shape or dimensions of the container or closure (immediate packaging) Nonsterile medicinal products: add tolerances to the height, width and depth for the registered dimensions of the 1L, 2.5L and 5L presentations of the immediate packaging of the finished product. (UK/V/0498/IB/004/G)	N/A	24 October 2017
Delete the non-significant parameter 'Total unknown impurities' from the specifications of the finished product. Minor changes to the test procedure for determination of impurities in the finished product to extend run time to 50 minutes. (UK/V/0498/IB/006/G)	N/A	14 November 2017

Change name of veterinary medicinal product from Starthrin to Fly Off (UK) / Ectofly (NL) (UK/V/0498/001/IB/003)	Module 1	15 November 2017
Change of RMS from UK to NL, change of procedurenumber from UK/V/0498/001 to NL/V/0255/001	Module 1	April 2018
MAH transfer from Cross Vetpharm Group Limited to Bimeda Animal Health Limited (National variations)	Module 1	November 2018
Change in the name of the manufacturers Change in the name and address of the MAH in the DDPS (NL/V/0255/IA/007/G)	N/A	11 November 2019
Renewal	N/A	10 October 2019