Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CLiK Extra 65 mg/ml Pour-On Suspension for Sheep

Date Created: November 2016

PuAR correct as of 05/07/18 when RMS was transferred to IE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0592/001/DC
Name, strength and pharmaceutical form	CLiK Extra 65 mg/ml Pour-On Suspension for Sheep
Applicant	Elanco Europe Ltd Lilly House Priestley Road Basingstoke Hampshire RG24 9NL
Active substance(s)	Dicyclanil
ATC Vetcode	QP53AX24
Target species	Sheep
Indication for use	Prevention of blowfly strike on sheep caused by *Lucilia sericata* or *Wohlfahrtia magnifica.*

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	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27/07/2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Ireland.

I. SCIENTIFIC OVERVIEW

CLiK Extra 65 mg/ml pour-on suspension for sheep contains dicyclanil, a well-known active substance, which has been authorised in the EU for up to 13 years.

The product contains 65 mg/ml dicyclanil to be administered at a guide dose rate of 0.6–2 ml (39–130 mg dicyclanil) per kg bodyweight; doses for specific weight ranges are included in the SPC.[1]

The product is indicated for the prevention of blowfly strike on sheep caused by *Lucilia sericata* or *Wohlfahrtia magnifica* and is recommended for treatment in sheep with any wool length, including off-shears. *Wohlfahrtia magnifica* is considered a minor use indication.

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 CONSTITUENTS

II.A. Composition

The product contains 65 mg/ml dicyclanil and the excipients methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, butylated hydroxytoluene, ponceau 4R, polysorbate 20, disodium edetate dihydrate distilled monoglycerides, triglycerides, propylene glycol, sodium hydroxide and purified water.

The container/closure system consists of white opaque polyethylene back pack containers closed with a polypropylene screw cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservatives 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 four step mixing and blending process.

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 dicyclanil an established active substance, the manufacture and control are satisfactorily described. 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.

European Pharmacopoeia monographs exist for polysorbate 20, methyl and propyl hydroxybenzoates, disodium edetate, butylated hydroxytoluene, medium-chain triglycerides, propylene glycol, sodium hydroxide and purified water. A USNF monograph exists for Carbomer copolymer. Satisfactory specification has been provided for the excipients not described in a pharmacopoeia.

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, pH, density, viscosity, identification, microbial purity, assays for Methyl hydroxybenzoate, propyl hydroxybenzoate, butylated hydroxytoluene and dicyclanil and degradation.

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.

Batches were stored under VICH[3] conditions of 25°C/60%RH, 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 and storage precautions provided in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 30 months
Shelf life after first opening the immediate packaging: 1 year.

Store in the original container.

Keep the container tightly closed, away from food, drink and animal feedstuffs.

Protect from direct sunlight.

Protect from frost.

[3] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Dicyclanil prevents the moult from the first to the second larval instar of *Lucilia* spp. It is less effective against later larval stages and does not have any adulticidal action. The mode of action of dicyclanil is believed to be similar to that of the triazine compounds.

The applicant has conducted studies which show that 7 days post-dosing, approximately 5% of the dose was absorbed and eliminated in urine and faeces. Peak blood levels were observed between 12 and 48h post dose, accounting for <0.025 mg dicyclanil equivalents/kg.

In experimental metabolism studies, absorbed drug was widely distributed throughout the body. Longest half-lives were found in liver and kidney being 13 and 10 days respectively. In muscle, fat and wool, unchanged dicyclanil was found to be the major residue, whereas in liver and kidney the descyclopropyl dicyclanil was found to be the major residue together with unchanged dicyclanil.

Toxicological Studies

The applicant has provided bibliographical data which show

- Single Dose Toxicity

The acute LD_{50} by the oral route in the rat was 520 mg/kg bodyweight (bw). The acute LD_{50} by the dermal route was greater than 2000 mg/kg bw in the rat. An acute inhalation toxicity study also conducted in the rat showed the acute LC_{50} to be 3184 mg/m^3 of air. The toxic effects were dyspnoea and reduced locomotor activity.

- Repeated Dose Toxicity

Repeated dose toxicity studies were carried out in rats and dogs. Rats were fed dicyclanil at various dose rates for 90 days the no observed effect level (NOEL) was 25 mg/kg feed/day equivalent to 1.6 mg/kg bw/day. Dogs were fed dicyclanil at various dose rates for three months. A NOEL could not be set for this study.

A dermal toxicity study was carried out in rats. Dicyclanil was applied to the skin at various dose rates for 28 days. The NOEL was 30 mg/kg bw.

A dietary toxicity study was carried out in dogs. Dicyclanil was administered at various dietary levels for 12 months. A NOEL of 25 mg/kg feed/day (equivalent to 0.71 mg/kg bw/day) was set.

- Reproductive Toxicity, including Teratogenicity:

A two-generation reproductive study was carried out in rats; the pup mortality in the high dose group was primarily confined to two specific litters. There was no other evidence of reproductive toxicity for this compound. Overall, the NOEL for

this study can be set at 30 mg/kg feed/day (equivalent to approximately 1.5 to 6.0 mg/kg bw/day).

Teratogenicity data were available from studies carried out in rats and rabbits. There was no evidence of teratogenic effects. In rats the NOEL was 5 mg/kg bw for dams and 25 mg/kg bw for foetuses and in rabbits 3 mg/kg bw for dams and 10 mg/kg bw for foetuses.

- Mutagenicity

There was no evidence of mutagenicity in four *in vitro* tests and one in vivo study.

- Carcinogenicity

Carcinogenicity data for dicyclanil was available from a 24-month study in rats and an 18-month study in mice. No carcinogenic effects were seen in rats. A tumorigenic effect was seen in mice at doses higher than the maximum tolerated dose (MTD). Therefore, this effect is regarded as not relevant for humans; however the exact mechanism of this finding was not clear. A NOEL was set at 25 mg/ kg feed/day in rats and 10 mg/kg feed/day in mice.

Studies of Other Effects

An expert report was provided which supported the conclusion that no specific investigations were needed to assess the effects of dicyclanil for immunotoxicity or neurotoxicity. The CVMP[4] summary report noted that dicyclanil can be considered non-irritant to eyes and skin.

Observations in Humans

Dicyclanil is not used in human medicine and therefore no information is available on observations in people.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that

- Redness and irritation may develop after skin or eye contact with the product.

Therefore the user warnings in the SPC are appropriate:

- Contact with skin and eyes should be avoided.
- Personal protective equipment consisting of synthetic rubber gloves and PVC trousers should be worn when handling the product.
- In case of skin contact remove contaminated clothing and thoroughly wash the affected parts of the body with soap and water.
- In case of eye contact wash immediately with clean water.

[4] The Committee for Medicinal Products for Veterinary Use.

- Always wash hands and exposed skin with soap and water after work.
- Do not eat, drink or smoke whilst using the product.
- Residues remain on the fleece for some time after treatment, therefore, it is good agricultural practice to minimise handling of sheep after treatment. If you need to handle sheep within 3 months after treatment, wear synthetic rubber gloves and long trousers or coveralls. If sheep are wet wear waterproof trousers.
- Do not shear sheep in the 3 months after treatment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

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 dicyclanil unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	•pH 5: 610 mg/l (buffer) •pH 7: 440 mg/l (buffer) •pH 9: 370 mg/l (buffer) •pH7: 350 mg/l (water)	Solubility was determined in three buffer solutions and in pure water at 25°C
Dissociation constants in water pKa	OECD 112	pKa: 4.58	
UV-Visible Absorption Spectrum	OECD 101	• major peak - 220 nm • minor peak - 260 nm	structure confirmed
Melting Point/Melting Range	OECD 102	250.5 - 252.4°C	with thermal decomposition

Study type	Guideline	Result	Remarks
Vapour Pressure	OECD 104	3.2 x 10^{-8} Pa (extrapolated)	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	•pH 5: 0.51 •pH 7.1: 0.69 •pH 9: 0.68	Log K_{ow} <4 indicates bioaccumulations studies are not required

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	K_{oc} of 89	Moderate mobility in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} 1.5 days (at 20°C)	Degradation of dicyclanil is considered to be a fast process with a half-life of 1.5 days

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test *Scenedesmus subspicatus*	OECD 201	EC_{50} (72 hr)	24 mg/l
Selenastrum capricornutum	OECD 202	EC_{50} (72 hr)	73 mg/l
Daphnia sp. Acute toxicity *Daphnia magna*	OECD 202	EC_{50} (24 hr)	17 mg/l
		EC_{50} (48 hr) nominal concentrations	8.3 mg/l
		EC_{50} (48 hr) measured concentrations	1.1 mg/l
Fish, acute toxicity *Oncorynchus mykiss*	OECD 203	LC_{50} (96 hr) nominal concentrations	60 mg/l
		LC_{50} (96 hr) measured concentrations	>100 mg/l
Lepomis macrochirus	OECD 203	LC_{50} (96 hr) measured concentrations	>68 mg/l
Earthworm/ *Eisenia fetida* reproduction	OECD 222	NOEC	At least 62.5 mg/kg
Dung fly larvae *Neomyia cornicina* (*Diptera: Muscidae*).	OECD 228	EC_{50}	0.1 mg/kg

Study type	Guideline	Endpoint	Result
Dung beetle *Euoniticellus intermedius*	OECD 122 Concept paper	NOEC EC_{50}	0.1 mg/kg 0.18 mg/kg
Dung beetle larvae *Aphodius constans*	OECD draft	 LC_{50} NOEC LOEC	Fresh Formulated 1.5 6.0 0.1 1.0 0.32 3.2

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)
Sheep	94	<0.01	0.46

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	72 h EC_{50} 24 mg/l	100	240 µg/l	2.21 µg/l (direct transfer)	0.009
Daphnia sp. immobilisation	48 h EC_{50} 1.1 mg/l	1000	1.1 µg/l	2.21 µg/l (direct transfer)	2.001
Fish, acute toxicity	96 h LC_{50} 60 mg/l	1000	60 µg/l	2.21 µg/l (direct transfer)	0.036
Earthworm reproduction	NOEC reproduction >62.5 mg/kg dry soil	10	6250 µg/kg dry wt	9.4 µg/kg (soil)	0.00015
Dung fly larvae	LC_{50} (larvae survival to adult flies) 0.01 mg/kg wet wt	100	0.1 µg/kg wet wt	200 to 540 µg/kg (dung)	2000 to 5400
Dung beetle larvae	EC_{50} (egg to adult development in week 1) 0.18 mg/kg fresh wt	100	1.8 µg/kg wet wt	200 to 540 µg/kg (dung)	111 to 300

A Tier B assessment was required to further refine the risk from dicyclanil on daphnia and chironomids (sediment dwelling organisms) the risk to dung insects is mitigated by the following recommendations in the SPC.

Dicyclanil has the potential to cause harmful effects on aquatic invertebrates and dung fly larvae.

Following use of this product, levels of dicyclanil potentially harmful to dung fly larvae have been shown to be excreted in faeces for approximately 4 weeks. Faeces from treated animals may temporarily reduce the abundance of dung fly larvae which may impact on dung degradation.

Test species	End point	AF	PNEC	PEC	RQ
Daphnia	21 day NOEC 27 µg/l	10	2.7 µg/l	58.5 µg/l	21.7
Chironomus	28 day NOEC 2.5 µg/l	10	0.25 µg/l		234

Adequate warnings have been included in the SPC.

The risk to aquatic organisms following fleece processing was evaluated. The risk of dicyclanil contamination of surface water following fleece processing is low. The use of the product should not adversely impact the environment as a result of wool processing.

III.B.2 Residues documentation

Residue Studies

Residue depletion studies using the final formulation have also been conducted in sheep. Samples of tissues were taken from animals at several time points. Results show that residues were not above the MRL in all tissues before the end of the withdrawal period, therefore a withdrawal period of 40 days is adequate to protect consumer safety.

MRLs

Dicyclanil is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues. The marker substance is Sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile.

MRLs are listed below:

Ingredients	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Dicyclanil	Sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile	Ovine	150 400 400 200	Fat Kidney Liver Muscle	Not for use in animals from which milk is produced for human consumption.

Withdrawal Periods

Based on the data provided, a withdrawal period of 40 day for meat in sheep justified. The product is not authorised for use in animals producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical information to show that only limited amounts of the active substance are absorbed transdermally after topical application to sheep. The systemically absorbed dicyclanil is rapidly eliminated within seven days, mostly in the urine after extensive metabolism, with some being eliminated via the faecal route. Efficacy and persistence of this efficacy have been demonstrated using the final formulation for the indications and duration stated in the SPC.

Tolerance in the Target Species

The applicant has provided a target animal tolerance study using an authorised reference product, CLiK 5% Pour-On Suspension, containing the same active substance. A placebo was used as a control. All doses were administered using a pour on applicator on three occasions. No adverse effects were seen following doses up to 4 times the recommended dose.

Resistance

The bibliography provided suggests that there have been no reports of clinically relevant resistance in blowfly from any part of the world.

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted dose determination studies which show that persistence efficacy of dicyclanil 6.5 mg/ml is 19 weeks.

Dose determination studies:

Study title	Preliminary efficacy evaluation of four formulations of dicyclanil, of different strengths, representing putative concentrations for the proposed product, in comparison with a positive control, CLiK Sheep Blowfly treatment (50 g/L dicyclanil) against experimental larval implants of the sheep blowfly *Lucilia cuprina*
Objectives	To determine the efficacy of four different formulations of dicyclanil against experimentally implanted blowfly larvae (*Lucilia cuprina*) in sheep at various times after treatment, as compared to a positive control
Test site(s)	New South Wales, Australia
Compliance with Regulatory guidelines	Good Clinical Practice (GCP) GCP and in line with WAAVP[5] guideline and the Australian guidelines for blowfly.
Test Product	Dicyclanil pour-on
Control product/placebo	Comparison product: Dicyclanil Spray Negative control (no treatment)
Animals	48 castrated male Merino sheep, 17 months old, with 7 weeks wool growth at treatment.
Outcomes/endpoints	An additional 2 weeks protection compared to a similar product with the same active ingredient.
Randomisation	randomised
Blinding	Semi-blinded
Method	The efficacy of the test products and control product were determined by comparing the survival of blowfly larvae on the treated sheep with that on the untreated controls.
RESULTS	The proposed product was effective against blowfly larvae *Lucilia cuprina* for up to four weeks longer than the comparison product.
DISCUSSION	The group treated with the 65 g/L formulation showed efficacy at 25 weeks, an efficacy of 0 at 26 weeks (larvae unaffected by the formulation) then demonstrated efficacy again at 27 and then sustained the highest rate of efficacy at 28 weeks post treatment.

Field Trials

The efficacy data for *Wohfahrtia,* was extrapolated from field trials using CLIK 5% Pour-on Suspension. This was accepted as Wohlfahrtiosis is considered a minor use indication, there are no reliable models for this parasite and new field studies are very difficult to perform due to variable levels of challenge.

Study title	Field Trial To Assess the Efficacy of CLiK for the Prevention of *Wohlfahrtiosis* on Sheep. Sotiraki *et al*
Objectives	Specific objectives/aims of the study

[5] The World Association for the Advancement of Veterinary Parasitology

Test site(s)	Crete
Compliance with Regulatory guidelines	There is no indication if this study was conducted in accordance with GCP, however it appears to have been well conducted and well reported.
Test Product	Dicyclanil 5% (w/v) Ready to Use (CLIK) was applied according to the authorised posology. Weighing 10 sheep from each treated group selected at random on day 0, and taking the arithmetic mean weight calculated dose volume.
Animals	2,570 healthy sheep from six flocks in two different areas of Crete. The sheep weighed between 28-53 kg and were aged 1 – 8 years.
Outcomes/endpoints	i) to determine the efficacy of dicyclanil against natural infection of *Wohlfahrtia magnifica* larvae when administered to rams which are the most susceptible group, when regular treatments and inspection are not feasible, in a spray on formulation under field conditions ii) to investigate the possibility that by treating males, and young non-milking females, it is possible to reduce fly pressure in such a degree to protect the whole flock.
Randomisation	Not specified
Method	If maggots were found, the sheep was classified as infected and marked. The maggots were removed from the sheep and preserved in 80% ethanol for further identification. The sheep was then removed from the trial population but left in the flock. Therefore, re-infestations were not counted. Climatic data including temperature and rainfall were obtained from a monitoring station located a few km away from each flock. After treatment administration and for at least 12 hours, all treated sheep were closely inspected by the Study Monitor and Co-investigator, then daily by the farmer for any change in general health, condition, behaviour and appetite.
Statistical method	The data were subjected to Chi-square analysis, and the survival curves from the Kaplan-Meier plot of hazard functions were compared by the Wilcoxan test.
RESULTS	
Outcomes for endpoints	The survival curves showed that the differences between the control and treated flocks in the incidence of infestations were statistically significant in males ($p<0.001$), non-milking females ($p<0.008$) and milking (untreated) females ($p<0.04$). There was a significant prevention in lambs in flock 1 in region 2, but not in other groups. With regard to the effect of the dicyclanil treatment on the whole flocks, when a limited number of sheep per flock were treated (males and non-milking females, approximately 15-20% of the flock) and not including

	lambs, the incidence in the treated flocks was significantly lower than in the control flocks ($p<0.0001$). Therefore final incidences in the test sites were approximately 13.5% in the control flocks compared to 4.5-5.5% in the treated flocks. The results showed that the reduction of infestation due to the application of CLIK was highly significant in rams ($p<0.004$), non-milking females ($p<0.02$) and milking females ($p<0.05$), but not in lambs ($pp<0.5$).
Adverse events	No adverse effects of treatment were recorded.
DISCUSSION	In this study, the environmental temperature declined to 19^{o}C in November, and no cases of myiasis were recorded in the treated sheep. A few cases were recorded in untreated milking ewes and in the untreated lambs in Region 1, group 2. There were 2 cases recorded in treated rams in September, but the majority of cases in the treated sheep occurred in October, indicating that the duration of protection of CLIK was coming to an end. The number of cases of myiasis was still significantly lower than in the control groups. CLIK provided protection for the treated sheep for approximately 14 weeks. Therefore prophylactic efficacy was demonstrated to be more than 90% for the treated sheep – the males and non-milking females. A degree of prophylaxis of 64% covered the untreated sheep; although this does not comply with The Guidelines on Specific Efficacy Requirements for Ectoparasiticides in Sheep, it shows that there was at least a halved incidence in the untreated sheep which improves welfare of these sheep. These sheep are routinely inspected twice a day at milking, therefore any infestations would be detected and rapidly treated.

Study title	Activity of Dicyclanil (CLIK) against myiasis caused by *Wohlfahrtia magnifica*: a multicentre clinical trial in sheep under mountain pasture summer management conditions.
Objectives	Activity of Dicyclanil (CLIK) against myiasis caused by *Wohlfahrtia magnifica*
Test site(s)	France, various locations.
Compliance with Regulatory guidelines	Not in accordance with GCP.
Test Product	CLiK (not otherwise specified) administered once.
Control product/placebo	Chlorhexidine digluconate 5%
Animals	1089 sheep (913 ewes, 168 lambs, 9 rams) of Tarasconaise, Pre-Alpes and Bsco-Bearnaise breeds were included. The sheep weighed 15-80kg and had a wool length of 0.50-15cm. At least two cases of myiasis had to be identified in the flock for the flock to be

	included in the study. No external antiparasitic had been administered in the 3 weeks prior to enrolment of healthy sheep, lambs, rams and non-milking ewes.
Outcomes/endpoints	Activity of Dicyclanil (CLIK) against myiasis caused by *Wohlfahrtia magnifica.*
Randomisation	Sheep were randomly allocated to a treatment group
Method	After treatment administration, the sheep were observed for a minimum period of 10 weeks (10-16 weeks). Larvae were collected from the first, fifth and tenth sheep with a positive infestation per flock, and then every ten infested sheep, to identify the parasite species. The maggots were collected, counted and kept in 90% alcohol for subsequent identification.
Statistical method	The primary analysis was calculated by comparing the area under the curve for each study location using an analysis of variance (ANOVA). The study duration was different between study locations so the AUC[6] was adjusted to a 10 week period. The secondary analysis was calculated analysing survival using a Cox regression model and a Log-Rank test. A homogeneity test between the categorical treatment variables and efficacy was performed using a Chi square test.
RESULTS	
Outcomes for endpoints	Overall 19 sheep out of 1089 (five treated with CLIK and 14 treated with control) were positive for *W. magnifica* and the majority of infestations were located in the sheep feet (72.7%), the rest were in the genital organs. Sixteen cases out of a total of 22 positive cases over the three sites (73%) were seen on one farm.
Adverse events	There were no adverse events recorded during the study
DISCUSSION	There were no significant differences between treatments where the AUC of % cumulative myiasis versus time were compared between treatments over a 10 week period (p=0.57). However, the overall total number of sheep with positive infestations was significantly lower in sheep treated with CLIK versus the control group. The homogeneity test using Chi square analysis showed that the number of animals with myiasis in the CLIK treatment (5/543) was significantly lower than in

[6] AUC: Area under the plasma drug concentration-time curve

	the control group (17/546) (p=0.010).

Study title	Clinical Field Study to evaluate the efficacy and safety of the proposed product A applied topically against blowfly strike in sheep in the UK.
Objectives	To evaluate the efficacy and safety of a new formulation containing dicyclanil (the proposed product) for long term prevention of body and breech strike on all classes of sheep under field conditions.
Test site(s)	This study was conducted in several areas of the UK to represent a range of geographic and climatic conditions.
Compliance with Regulatory guidelines	The study was conducted according to GCP and in line with EMEA/CVMP/411/01-Final, WAAVP guideline for evaluating the efficacy of ectoparasiticides against myiasis causing parasites on ruminants.
Test Product	A-20208 (dicyclanil) administered once.
Control product/placebo	Negative control (no treatment).
Animals	3600 sheep aged 2 months - 8 years, various breeds and wool length and of either sex. Animals with faecal contaminated back-ends were dagged on day 0 prior to treatment and the dagging was recorded.
Outcomes/endpoints	The prevention of body and/or breech strikes (as defined in 'observations' above) caused by the sheep blowfly (*Lucilia sericata*) for a defined time period and was determined by percentage strike rates (sr) comparison of study groups, as well as time to reach the limit of protection in the treated group (>2%sr).
Randomisation	Randomised. All sheep enrolled were randomised into treatment groups and treated with either the test product (2391) or remained untreated (1209) on day 0.
Blinding	Non-blinded.
Method	The test product was administered to the sheep as a pour-on using a calibrated pour-on applicator with a fan spray nozzle and was sprayed on to achieve treatment bands of approximately 10-15 cm width across the back and breech. The product was applied holding the gun approximately 45 cm from the sheep. It was applied as a fan spray along the backline of the animal in bands 10-15 cm wide from the middle of the shoulders and in an arc around the crutch and tail. Half the dose was applied along the backline with the remainder over the tail and crutch area. The treatment applicator was recalibrated after approximately half the sheep had been treated at each site and each treatment group if lambs and ewes were treated. The dose administered per animal ranged from 20-36

	ml per animal. All study sites had barn facilities and at most sites the animals were treated under cover and held there for an hour post treating if rain threatened to allow the test product to dry on the fleece.
Statistical method	Power calculation based on the Fisher exact test. The statistical unit was the experimental group at each site and pooled for all sites if central values of groups are compared. α=0.05. Statistical analysis was conducted for each site as well as for pooled data of all sites.
RESULTS	
Outcomes for endpoints	• Strikes were observed at some sites from week 1. Week 13 was the first time point when the % strike rate (pooled data) was >2% in the untreated group, compared to the treated group where this threshold was not reached at the study end (week 22). The duration of protection in the treated group can be considered as 19 weeks, since week 19 was the last occurrence of strikes in the untreated group. • At the other 8 sites, the cumulative strike rate at study end (22 weeks after treatment) in untreated sheep ranged from 0.8% to 20.5% with a mean of 8.1%; in treated sheep the mean was 0.6%. • Strikes occurred mostly from week 11 until week 20 as evidenced by new strikes in the treated or untreated sheep. • When the individual sites are reviewed, the efficacy (prevention of strike) of the treatment was >98% up to week 22 on all sites, when the study concluded. In comparison, the threshold of >2% strikes was exceeded in weeks 11-13 in the untreated group. • The differences in strike time curves between the two study groups were of significance for single sites with strike occurring ($p<0.05$). The differences in strike time curves between the two study groups were of significance for pooled sites ($p=0.0001$). In all cases % strike rates in the untreated control group were equal to or higher than % strike rates in the treated group. • Across all sites, the % strike rates (based on the Kaplan-Meier approach) at end point were 6.68 and 0.46 for untreated and treated groups respectively. • The treated group (based on Cox proportional hazard analysis) had a 0.068 times lower strike risk than the untreated group, (0.036-0.127; 95% confidence limit), this difference was statistically significant ($p=0.001$). The interpretation is that one has to expect about 14.7 times more struck animals in the untreated group. The distribution of strike time among the two groups was significantly different ($p=0.0001$).

Adverse events	708 animals showed at least one adverse event (serious or non-serious) across all sites and both treatment groups: 482 in the test product group and 226 in the untreated group. The percentage of animals showing at least one adverse event was 19.8% and 20.6% in the untreated control group and test product treated group respectively. The group difference is not significant ($p>0.62$). All non-serious adverse events were considered to be unrelated to treatment.
DISCUSSION	This study provides evidence to support the safety and efficacy of the CLiK Extra 6.5% product for a persistent period of 19 weeks when used in the field at the recommended dose and when applied as proposed in the SPC to prevent the crutch and body strikes caused by the sheep blowfly, *Lucilia sericata*, in the UK.

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)