IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

CLiKZiN 12.5 mg/ml Pour-On Suspension for Sheep

PRODUCT SUMMARY

EU Procedure Number	IE/V/0427/001
Name, Strength, Pharmaceutical Form	CLiKZiN 12.5 mg/ml Pour-On Suspension for Sheep
Active Substances(s)	Dicyclanil
Applicant	Elanco GmbH Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Sheep
Indication For Use	Prevention of blowfly strike on sheep due to *Lucilia sericata*.
ATC Code	QP53AX24
Legal basis of original application	Application in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original decentralised procedure	02 June 2010 (UK) 24 September 2010 (IE)
Concerned Member States for original procedure	France Ireland Netherlands Portugal Spain Added via change of RMS: UK

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

CLiKZiN 1.25% (W/v) Pour-On Suspension for Sheep is authorised for use in sheep for the prevention of blowfly strike due to *Lucilia sericata*. The dosage rate of dicyclanil is 7.5 - 25 mg per kg bodyweight, corresponding to 0.7 - 2 ml of product per kg bodyweight. The product must be applied with a manual or automatic dosing gun, fitted with a spray nozzle, which guarantees the correct spreading of the product on the fleece and should be administered before or at the start of predicted fly activity but is also suitable for use during the fly season. The product is packaged in pigmented white opaque polyethylene back pack container with blue polypropylene screw cap, containing 0.8, 2.2 or 5 litres of product.
The application was made in accordance with article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC.
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; the slight 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 of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.[1] SPC - Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains the active substance dicyclanil (INN) and excipients quinoline yellow (E104), patent blue V (E131), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), butylated hydroxytoluene (E321), polysorbate 20, acrylic acid copolymer, disodium edetate, distilled monoglycerides, triglycerides (medium-chain), propylene glycol, sodium hydroxide and purified water.
The product is presented in pigmented white opaque polyethylene back pack container in volumes of 0.8, 2.2 and 5 litres, closed with blue polypropylene screw cap. The particulars of the containers and controls performed are provided and conform to the current guidelines.
The choice of formulation is justified.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

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.

C. Control of Starting Materials

The active substance, dicyclanil, has no monograph in the European Pharmacopoeia. The manufacturer provided details of a testing monograph, and this was considered acceptable. The active substance is manufactured in accordance with the principles of good manufacturing practice.
All excipients except quinolone yellow (E104), patent blue V (E131), acrylic acid copolymer and triglycerides are described in the Ph. Eur. The applicant has provided detailed in-house specifications for quinolone yellow (E104) and patent blue V (E131). The applicant has provided raw material specifications for acrylic acid copolymer and triglycerides, comprising tests of appearance, identity, loss on drying and carboxylic acid content and heavy metals. This is considered acceptable.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

F. 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.

G. 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. The shelf-life of the veterinary medicinal product as packaged for sale is 2 years. An in-use shelf life of 12 months is justified.

H. Genetically Modified Organisms

Not applicable

J. Other Information

A shelf life of 3 years[1] and in-use shelf life of 12 months is justified, subject to the following storage warnings:

- Protect from direct sunlight.
- Protect from frost.
- Store in tightly closed original containers, away from food, drink and animal feedstuffs.

[1] Shelf-life of the veterinary medicinal product as packaged for sale changed from 24 to 36 months.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The data submitted for this application was cross-referred to the CVMP Summary Reports. The CVMP summary report indicates that dicyclanil has a long lasting action which interferes with moulting and pupation in dipteran species. However, the precise mode of action of this compound on ectoparasites is not known. A variety of *in vitro* and *in vivo* pharmacodynamic tests were performed with dicyclanil in rats, mice and guinea pigs. In vitro, dicyclanil was devoid of significant effects on the neuromuscular junction at concentrations below 3 mM. Slight antagonistic effects on smooth muscle were reported at concentration levels above 0.1 mM. Dicyclanil caused a statistically significant increase in heart rate, tidal volume and minute volume at a dose level of 100 mg/kg bodyweight in studies on the cardiovascular and respiratory systems in the rat. In various *in vivo* studies, dicyclanil was devoid of significant effects on behaviour at a dose level of 1 mg/kg bw in mice.

In the rat, the absorption, distribution, metabolism and excretion profile of 14C-labelled dicyclanil was investigated following repeated oral administration of test compound at dose levels of either 0.5 or 20 mg/kg bodyweight for a suitable number of days. At least 80% of the administered dose was absorbed from the gastrointestinal tract irrespective of sex or dose level. Approximately 93% of the dose was excreted in the first seven days of dosing (80% via the kidneys). In the following 48 hours, only an additional 2 to 3% was excreted. Biotransformation was initiated by oxidative cyclopropyl-ring opening at various positions, with further oxidation occurring in some cases. The cyano group of this compound was metabolically stable. The major metabolite recorded in urine, accounting for approximately 50 to 55% of the administered dose (low and high dose levels) was a secondary propionic acid amide, N-(4,6-diamino-5-cyano-pyrimidin-2-yl)-propionamide. The metabolite 2,4,6-triamino-pyrimidine-5-carbonitrile accounted for approximately 11% of the dose, whilst unchanged dicyclanil represented 2% (low dose) and 7% (high dose) of the administered dose. Faecal metabolites appeared in various fractions including unchanged dicyclanil, but no single fraction accounted for more than 3% of the total dose. Besides polar metabolites, 2,4,6-triamino-pyrimidine-5-carbonitrile was the major metabolite recorded in liver and kidney, with lower amounts of parent

compound and probably N-(4,6-diamino-5-cyano-pyrimidin-2-yl)-propionamide.
The pattern was similar for muscle and fat, except that these latter tissues contained more non-polar metabolites as a percentage of the total residue, especially so in the case of fat.
Tissue residue levels were measured up to 3 days following the completion of 7 consecutive daily oral doses of radiolabelled dicyclanil at dose levels of either 0.5 or 20 mg/kg bw. Twenty-four hours following the final dose (0.5 mg/kg bw treatment group), the mean residue concentrations for dicyclanil were below 4 mg dicyclanil equivalents/kg, except in the liver (300 mg/kg), blood (200 mg/kg), kidney (40 mg/kg) and residual carcass (20 mg/kg). The residual radioactivity in blood was associated with red blood cells. At the higher dose level (20 mg/kg bodyweight), the tissue residues were accordingly higher (10 to 60 times) and demonstrated a similar distribution pattern. The highest residues were recorded in liver (approximately 5000 mg dicyclanil equivalents/kg). Within 72 hours following the last dose, the residues declined to values of about 30 to 80% of those at the first time point, except for whole blood, where the residue levels remained nearly constant during this period.

Toxicological Studies

The applicant has cross-referred to the CVMP summary report which show that relevant toxicity issues have been addressed with regard to single and repeated dose toxicity, tolerance, reproductive toxicity, mutagenicity, carcinogenicity, and other appropriate parameters.
Single Dose Toxicity
A study was performed to check the acute toxicity of dicyclanil following single oral administration. The results indicated that the acute LD_{50} when delivered orally to rat was 520 mg/kg bw. The acute LD_{50} by the dermal route was greater than 2000 mg/kg bodyweight in the rat. An acute inhalation toxicity study also conducted in the rat which showed the acute LC_{50} to be 3,184 mg/m^3 of air. The toxic effects were dyspnoea and reduced locomotor activity.
Repeated Dose Toxicity
Repeated dose toxicity studies were performed in rats and dogs. A NOEL[1] has been identified as being 5 mg/kg bodyweight in a 28 day dermal toxicity study and 25 mg/kg feed/day (equivalent to 1.6 mg/kg bw/day) in a 90 day dietary toxicity study in rats.
A NOEL of 25 mg/kg feed/day in a 12 month dietary toxicity study was reported in dogs.
Reproductive toxicity
A two generation reproductive study was conducted in rats. A suitable number of rats were used in the study and dicyclanil was administered at 0, 5, 30, 200 and 500 mg/kg feed/day. The treatment was continued until the end of the lactation period.
There was no other evidence of reproductive toxicity for this compound.
Embryotoxicity/ foetotoxicity (inc. teratogenicity)

Reports of studies on reproductive toxicity/teratogenicity were provided. A study conducted in rats at daily dose levels of 0, 1, 5, 25 and 75 mg/kg between days 6 and 5 of gestation showed no evidence of teratogenic effects. Another study in rabbits noted no indication of any teratogenic potential at dose levels of 0, 1, 3, 10 and 30 mg/kg bodyweight between days 7 and 19 of gestation.

Mutagenicity

Dicyclanil didn't show any mutagenic potential in a range of *in vitro* tests.

Other Studies

The CVMP Summary Report indicated no evidence of immuotoxic effects in repeated-dose oral toxicity studies in dogs. Dicyclanil can be considered non-irritant to the eye and skin and was shown to have a low sensitization potential in guinea pig following epidermal challenge after intravenous exposure. The effects on the central nervous system were only observed in the 3-month dog study at the highest dose of 1500 ppm. One dog showed convulsions and died at week 11 and other animals showed ataxia, shaking and unnaturally raised tails. There was no neurotoxicity effects observed in the 1-year dog study in the extensive neurological examinations, even at the high feeding dose of 750ppm.

Observations in Humans

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. The use of Clikzin 1.25% (w/v) Pour-on Suspension for Sheep is not expected to present an undue hazard to the user. The product literature and SPC contain the following safety warnings:

- Operators should wear synthetic rubber gloves and PVC trousers when applying 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.
- Always wash hands and exposed skin with soap and water after work.
- Do not eat, drink or smoke whilst using the product.
- It is good agricultural practice to minimise handling of sheep after treatment. If you need to handle sheep within 2 months after treatment, wear synthetic rubber gloves and long trousers or coveralls. If sheep are wet wear waterproof trousers.

Ecotoxicity

The applicant provided a Phase II environmental risk assessment in compliance with the relevant guidelines.

The predicted no effect concentration (PNEC) values derived from several studies were acceptable and in accordance with VICH guidelines.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The product literature highlights the fact that the product is extremely dangerous to fish and aquatic life, and that care must be taken not to contaminate surface waters or ditches with the product or used container.

III.B Residues documentation

Residue Studies

The applicant submitted four GLP-compliant residue depletion studies to investigate residue depletion following administration of the product. The product was administered topically in a single dose to animals which were slaughtered at various time points. Samples of edible tissues were taken from animals at several time points, and results showed that residues depleted to below the maximum residue limit (MRL) in all tissues before the end of withdrawal period.
The analytical method was HPLC, and the method was fully validated. Residues were below the MRLs for the relevant tissues in all samples collected before the authorised withdrawal period.

MRLs

	MRL (µg/kg)
Muscle	200
Liver	400
Kidney	400
Fat	150

Withdrawal Periods

The following withdrawal period is acceptable based on the results of the residue depletion study report submitted by the applicant.
Meat and offal: 7 days
Milk: Do not use on sheep producing milk for human consumption.
[1] No Observed Effect Level

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

The applicant provided a review of published literature on the pharmacodynamics and pharmacokinetics of the active substance. The information provided is considered satisfactory and supports information in section 5.1 of the SPC

Pharmacology

Pharmacodynamics

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 adulticide action.

The mode of action of dicyclanil is believed to be similar to that of the triazine compounds.

Pharmacokinetic particulars

In studies with a more concentrated 5% (w/v) formulation, after 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 radioactivity 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.

In field residue depletion studies on sheep with the veterinary medicinal product, residue levels at day 7 were very low (at maximum 31.9 and 30.7 µg/kg in liver and kidney, respectively, and no quantifiable residues found in muscle or fat), indicating minimal systemic absorption.

Tolerance in the Target Species of Animals

The applicant has provided eight literature references which show that product is well tolerated in the target species. However, no target species tolerance study was conducted using the product in accordance with *either the Notice to Applicants Volume 7 'Evaluation of the Safety of Veterinary Medicinal Products for the Target Animals' 1994, or with the VICH GL 43 'Target Animal Safety for Veterinary pharmaceutical products' July 2008*. The applicant relied on the target species tolerance study presented for the original Clik 5% pour-on suspension MA application. Clik 5% pour-on suspension contains 5% dicyclanil. The appropriate warnings are listed on the SPC and product literature. This is considered acceptable.

Resistance

The applicant has provided the summary of the reports of SLEE[1]. The UK results suggested that after the spike increase in SLEE reports in 2007, the SLEE reported in 2008 and 2009 have reduced. This is low incidence and not an indication of resistance issue. This is considered acceptable.

IV.B Clinical Studies

The applicant provided a review of published literature and in addition provided reports on various clinical studies conducted with the product containing dicyclanil. Dose determination study was carried out in accordance with EU guidelines on Good Clinical Practice. The animals involved in the studies, except the control animals, were infected with a number of parasitic larvae and all sheep were subsequently treated with the test formulation. The animals were observed daily for evidence of adverse reactions or illness. The studies established the efficacy of the product.

[1] Suspected Lack of Expected Efficacy

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.