IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Spotinor 10 mg/ml Spot-on Solution for cattle and sheep

PRODUCT SUMMARY

EU Procedure number	IE/V/0544/001 (formerly UK/V/0478/001)
Name, strength and pharmaceutical form	Spotinor 10 mg/ml Spot-on Solution for cattle and sheep
Active substances(s)	Deltamethrin
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target species	Cattle,Sheep
Indication for use	For the treatment and prevention of infestations by lice and flies on cattle; ticks, lice, keds and established blowfly strike on sheep and lice and ticks on lambs. On cattle**:** For the treatment and prevention of infestations by both sucking and biting lice, including *Bovicola bovis, Solenopotes capillatus, Linognathus vituli* and *Haematopinus eurysternus* in beef and dairy cattle. Also as an aid in the treatment and prevention of infestations of both biting and nuisance flies including *Haematobia irritans*, *Stomoxys calcitrans, Musca* species and *Hydrotaea irritans*. On sheep: For the treatment and prevention of infestations by ticks *Ixodes ricinus* and by lice (*Linognathus ovillus, Bovicola ovis*), keds (*Melophagus ovinus*)and established blowfly strike (usually *Lucilia spp*). On lambs: For the treatment and prevention of infestations by ticks *Ixodes ricinus* and by lice *Bovicola ovis*.
ATCvet code	QP53AC11
Date of completion of the original decentralised procedure	18 June 2014 (UK) 05 September 2014 (IE)
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden UK added via RMS change

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

Spotinor 10 mg/ml Spot-on Solution for Cattle and Sheep has been developed as a generic of Pfizer Spot-on 1% w/v for Cattle and Sheep, which has been authorised in the UK since 1984. Spotinor is considered to be pharmaceutically equivalent to the reference product therefore bioequivalence can be assumed and studies are not required.

The product is indicated for the control of lice and flies on cattle; ticks, lice, keds and established blow fly strike on sheep; and lice and ticks on lambs. The product is administered topically and applied along the midline of the back. The product is contraindicated in convalescent or sick animals and in non-target species. It should not be used in cases of known hypersensitivity to the active or the excipient.

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 of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition
The product contains deltamethrin as the active substance and excipients are medium-chain triglycerides.

The container/closure system consists of a 250 ml, 1 x 500 ml and 2 x 500 ml clear high-density polyethylene bottles with internal graduated calibration chamber and a white screw polypropylene cap. 1 litre and 2.5 litre white high density polyethylene back pack for use with a suitable dosing device and a white screw polypropylene cap. 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. The product is manufactured by mixing the medium chain triglycerides and the deltamethrin until complete dissolution is achieved. The product is then filled into the packaging containers. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials
The active substance is deltamethrin, an established active substance described in the British Veterinary Pharmacopoeia. Data on the active substance have been supplied in an Active Substance Master File. 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.

The excipient is manufactured in compliance with the relevant Ph. Eur. Monograph. Certificates of analysis have been provided.

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. The tests include those for identification and assay of the active substance, appearance, identification of impurities, water content, specific gravity and microbial quality.

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.

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. A retest period of 2 years is supported.

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. Data were provided for batches stored at 25°C/60% RH and 30°C/65% RH for 24 months. In addition accelerated studies were performed and data were provided for batches stored at 40°C/75% RH for 6 months. A shelf life of 2 years has been established.

In-use stability studies were also performed. Following removal of the half the contents from the packaging, the cap was replaced and the pack stored at 25°C/60% RH or 30°C/65% RH for 6 months. An in-use shelf life of 6 months is supported.

G. Other Information

- Shelf life of the finished product as packaged for sale: 3 years.
- Shelf life after first opening the immediate packaging: 6 months
- Store the dispenser bottle in the outer carton in order to protect from light.
- Do not freeze.
- Store below 25°C.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Deltamethrin is an ectoparasiticide belonging to the pyrethroid type II class. It works by affecting neurotransmission in the target parasite, exerting an action on axonal sodium channels. Deltamethrin interferes with sodium and potassium channels in both the peripheral and central nervous system causing prolonged depolarisation and hyperexcitability of the nerve membrane. This results in repetitive firing of the nerve, including increased and sustained action potentials which overwhelm the muscular neurotransmitters, which leads to paralysis and death of the parasite.

The effects of deltamethrin tend to be reversible up to doses of 0.1 mg/kg/bw. Pyrethroids are highly hydrophobic compounds, have low water solubility and are lipophilic. This means they tend to concentrate in fat and skin, with fat residues more persistent than in other tissues.

Pharmacokinetics

Following dermal application, deltamethrin is only slightly absorbed through the skin. This means deltamethrin remains available to the target ectoparasites and is therefore effective as a topical ectoparasiticide.

Deltamethrin applied topically has been shown to move from the back to the lower body within 24 hours of application. In a study with radiolabelled deltamethrin pour on, the majority of the product (72%) remained at the site of application 24 hours after application. Blood levels of radioactivity remained low and <1.5% were detected in excreta.

Deltamethrin is metabolised through oxidative and neurotoxic pathways. Following absorption deltamethrin is excreted via the faeces. The compound is completely eliminated within 6-8 days following oral administration.

Toxicological Studies

As this is a generic application submitted according to Article 13 (1) of Dricetive 2001/82/EC as amended and bioequivalence with the reference product can be assumed, the results of toxicological studies are not required. However a literature review was performed in support of the application.

- Single Dose Toxicity

Following oral administration to rats and mice LD_{50}[1] values of 30-50 mg/kg bw and 20-30 mg/kg bw respectively were determined. Dermal toxicity in rats is considered negligible and no toxic signs were seen, this is likely to be due to poor absorption.

- Repeated Dose Toxicity

In rats, dogs and mice the overall NOEL[2] following oral administration was determined to be 1 mg/kg bw. In dogs signs of systemic toxicity were seen following oral administration of high doses of deltamethrin. The signs included weight loss, vomiting and neurological clinical signs such as unsteady gait and trembling.

- Reproductive Toxicity, including Teratogenicity:

The submitted studies indicate deltamethrin has no effects on fertility and foetotoxicity was not seen in doses up 3 mg/kg bw/day. Some effects, including neurological impairment, were seen in parents and pups following oral administration of a very high dose (320 mg/kg bw).

- Mutagenicity

In vivo tests in mice did not demonstrate any genotoxic potential of deltamethrin.

- Carcinogenicity (if necessary):

Combined long term toxicity / carcinogenicity studies in rats and mice were reviewed. No carcinogenic effects of deltamethrin were observed.

Studies of Other Effects
Studies in rats and rabbits indicate deltamethrin has potential skin irritant and eye irritant properties. Transient effects such as moderate erythema, conjunctival irritation and corneal clouding were observed following topical application to the skin or eyes.

Observations in Humans
Reports detailing effects following skin contamination were reviewed. Deltamethrin caused skin sensitisation in 90% of people exposed and paraesthesia in the legs, mouth and tongue. Recovery within 48 hours is seen following symptomatic treatment. No clinical or haematological changes have been observed in operators repeatedly exposed to deltamethrin during field applications.

In addition a double blind patch test in human volunteers resulted in a slight skin irritation. The irritation lasted no more than an hour and no skin damage was observed.

User Safety
A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely route of exposure is dermal through accidental spillage onto skin. There is also the possibility of ocular or oral through accidental splashing or hand to mouth transfer. The product presents the same risks to the user as the reference product; therefore the same warnings are included on the SPC and product literature. These precautions are adequate to ensure safety to users of the product.

- Persons with known hypersensitivity to the product or one of its components should avoid contact with the veterinary medicinal product.
- Wear protective clothing including waterproof apron and boots and impervious gloves when either applying the product or handling recently treated animals.
- Remove heavily contaminated clothing immediately and wash before use.
- Wash splashes from skin immediately with soap and plenty of water.
- Wash hands and exposed skin after handling this product and before meals.
- In case of contact with eyes, rinse immediately with plenty of clean, running water and seek medical advice.
- In case of accidental ingestion, wash out mouth immediately with plenty of water and seek medical advice.
- Do not smoke, drink or eat while handling the product.
- This product contains deltamethrin which may produce tingling, itchiness and blotchy redness on exposed skin. If you feel unwell after working with this product, consult your doctor and show this label.
- To the physician: Advice on clinical management is available from the National Poisons Information Service.

Environmental Safety

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

Phase I:

The product is a cutaneous spot-on solution for use in cattle and sheep. Due to the use of the product, there is the potential for deltamethrin to be released into the environment.

The initial predicted environmental concentration (PEC) in soil was calculated for each of the target species. In beef cattle, dairy cattle, sheep and lambs the PEC_{soil} was less than 100 µg/kg. However, 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 unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result	Remarks
Water solubility (at 20°C)	OECD 105	0.005 mg/l	Published source
Dissociation constants in water pKa	OECD 112	N/A	N/A
UV-Visible Absorption Spectrum (nm)	OECD 101	264	Published source
Melting Point/Melting Range (°C)	OECD 102	98 - 101	Published source
Vapour Pressure (Pa)	OECD 104	1.0×10^{-6}	Published source
n-Octanol/Water Partition Coefficient ($logP_{ow}$)	OECD 107	>6.5	$logP_{OW}$ >4, indicates potential for bioaccumulation

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	133618 K_{oc} (Geometric mean of 5 soils)	Non-mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} (20°C) = 44 - 187 days, (geometric mean = 76 days) Soil DT50 (12°C) geometric mean = 163 days	DT_{90} <1 year

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC_{50}[3]	>5.4 µg/l
Daphnia spp. immobilisation	OECD 202	EC_{50}	0.15 µg/l
Sediment invertebrate in *Chironumus riparius*	OECD 218 & 219	LC_{50}	11 µg/l
Fish, acute toxicity in *Oncorhynchus mykiss*	OECD 203	LC_{50}[4]	0.7 µg/l
Earthworm*/Species* sub-acute/reproduction	OECD 220/222	NOEC[5]	1500 µg/kg
Dung fly larvae	OECD 228	EC_{50}	0.1 mg/kg_{dwt}
Dung beetle larvae	OECD draft	EC_{50}	0.02 mg/kg_{dwt}

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.

Target animal	PEC					

	Soil	Dung	Groundwater	Surface water, run-off	Surface water, direct excretion	Sediment
	(µg/kg)		µg/l			$\mu g/kg_{dwt}$
Dairy Cow	1.43	400			0.000059***	0.15 0.40
Beef Cattle	3.76				0.00016***	0.41 1.05
Sheep	3.02	N/A			-	-
Lambs	5.00*		<0.000001**	0.00018	-	-

*Initial PEC_{soil} used to calculate groundwater and surface water PECs
**PEC_{gw} refined using FOCUS PEARL
***$PEC_{swdirectexcretion}$ 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}= >5.4	100	0.054	0.00018	<0.03
Daphnia sp. immobilisation	EC_{50} = 0.15	1000	0.00015	0.00018	1.2
Fish, acute toxicity	LC_{50} = 0.7	1000	0.0007	0.00018	0.26
Earthworm reproduction	NOEC = 1500	10	150	5.0	0.03
Dung fly larvae	EC_{50} = 100	100	1	400	400
Dung beetle larvae	EC_{50} = 20	100	0.2	400	2000

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

As the RQ[6] 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). A model was presented for predicting conservative deltamethrin environmental concentrations in sediment. The model demonstrated the $PEC_{sediment}$ to drop below the sediment dweller (Chironomid) PNEC of 0.26 µg/kg on Day 17 when a worst case scenario of 3 days treatment is considered. Therefore, a 2 to 4 week exclusion period, to mitigate the potential risk indicated for sediment dwelling organisms, is appropriate. As a result, the following risk mitigation measures pertaining to dung organisms and aquatic invertebrates were included on the SPC and product literature.

- 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 cattle away from water bodies for four weeks 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

Residue studies have not been submitted. The proposed product formulation is qualitatively and quantitatively the same as the reference product. Therefore identical withdrawal periods were proposed and no further studies were required.

Withdrawal Periods

Cattle

Meat and offal: 17 days

Milk: zero hours

Sheep

Meat and offal: 35 days

Milk: Not authorised for use in ewes producing milk for human consumption.

[1] LD_{50} – Dose that kills 50% of the population

[2] NOEL – No observable effect level

[3] EC_{50} – Half the maximal effective concentration

[4] LC_{50} – The concentration that kills half a sample population

[5] NOEC – No observable effect concentration

[6] RQ – Risk Quotient = PEC/PNEC

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed, the results of pharmacological studies are not required. A literature review was provided in support of the application and the information provided is summarised in Section III.

Tolerance in the Target Species

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be accepted, the results of tolerance studies are not required.

Resistance

A literature review was performed and appropriate risk mitigation measures have been considered. Resistance to pyrethroids has been identified in sheep and cattle. Synthetic pyrethroids were released onto the market in 1981 and resistance had developed by 1985. The resistance is thought to develop through selection, often due to suboptimal conditions and lice not being exposed to adequate concentrations of deltamethrin. Mutations of insect sodium channels which confer resistance have also been identified.

It was concluded that resistance to deltamethrin is present and in order to slow down resistance, periodic relaxation of selection pressures is required. Ideally as few chemicals are used and non-chemical control methods are applied instead. In addition alternating between unrelated compounds will also slow the development of resistance. Adequate warnings and precautions appear on the SPC and product literature.

- To avoid resistance, the product should only be used if the susceptibility of the local fly population to the active substance is assured.
- Cases of resistance to deltamethrin have been reported in stinging and nuisance flies in cattle and lice in sheep.
- The product will reduce the number of flies resting directly on the animal but it is not expected to eliminate all flies on a farm. The strategic use of the product should, therefore, be based on local and regional epidemiological information about susceptibility of parasites, and used in association with other pest management methods.
- Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:

- too frequent and repeated use of ectoparasiticides from the same class over an extended period of time;
- underdosing which may be due to underestimation of bodyweight, misadministration of the product, or lack of calibration of the dosing device.

IV.II. Clinical Documentation
Laboratory Trials
As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be accepted, the results of 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