ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Deltafort 10 mg/ml Pour-on Solution

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Deltafort 10 mg/ml Pour-on Solution
Applicant	Virbac S.A. 1'ere Avenue, 2065m – LID 06516 Carros Cedex France
Active substance(s)	Deltamethrin
ATC Vetcode	QP53AC11
Target species	Cattle and sheep
Indication for use	As a topical application for the control of lice and flies on cattle; ticks, lice, keds and established blowfly strike on sheep and lice and ticks on lambs. Cattle: For the control of both sucking and biting lice, including *Damalinia bovis, Solenopotes capillatus, Linognathus vituli* and *Haematopinus eurysternus* on all ages of cattle including dairy cattle producing milk for human consumption. Also as an aid in the control of both biting and nuisance flies including *Haematobia irritans, Stomoxys calcitrans, Musca* species and *Hydrotaea irritans*. Sheep: For the control of ticks *Ixodes ricinus* and of lice and keds and established blowfly strike. Lambs: For the control of ticks *Ixodes ricinus* and lice *Bovicola ovis*.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

Deltafort 10 mg/ml Pour-on Solution is an ectoparasiticide containing deltamethrin, a synthetic pyrethroid. The product has been developed as a generic of Pfizer Spot On Insecticide 1% w/v Cutaneous Solution and bioequivalence is claimed with this product. The product is applied topically to cattle, sheep and lambs at a dose of 10 ml, 5 ml and 2.5 ml respectively.

Deltafort is indicated for the control of lice and flies in cattle as well as the control of ticks, lice, keds and blowfly strike in sheep. The product is also licensed for treatment of lice and tick infestation in lambs. The product should not be used in animals with known hypersensitivity to the active or excipients and is also contraindicated for use in sick or convalescent animals.

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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains deltamethrin as active substance and triglycerides (medium-chain) as excipients.

Packaging consists of a 500 ml and 1 litre white high-density polyethylene bottle with a removable aluminium seal, a HDPE cap and a PP dosing device equipped with a measuring chamber delivering doses of 2.5 ml, 5 ml and 10 ml, placed in a carton box. A 2.5 litre white high-density polyethylene bottle with a removable

[1] SPC – Summary of Product Characteristics

aluminium seal, a PP cap and a PP coupling vented cap. A 2.5 litre or 4.5 litre multi-layer PET/aluminium/PA/PE flexible pouch with a PP cap and its specific coupling POM “E-lock”, placed in a carton box.

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.

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. The product is manufactured by mixing the excipients with the active substance until dissolution is complete and then filling the containers.

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 was supplied in the form of an Active Substance Master File (ASMF) from one manufacturer and an in-house specification was provided for the other active substance manufacturer. 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 triglycerides, medium-chain, complies with the respective Ph. Eur monograph. Batch analysis data demonstrating compliance have been provided.

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

Not applicable.

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. The tests include identification of the active substance, identification of impurities, visual appearance and microbiological purity.

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.

G. 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 12 months has been established for both manufacturers of the active substance.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf-life of the finished product as packaged for sale: 3 years
- For bottles only: Shelf-life after first opening the immediate packaging: 1 year
- For pouches only: Shelf-life after first opening the immediate packaging: 2 years

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which describes the various means by which deltamethrin may come into contact with the user, including accidentally splashing the product and misusing the product resulting in leaking or spillage. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the 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.
- **Advice to medical practitioners**: Advice on clinical management is available from the National Poisons Information Service.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required for cattle and sheep raised on pasture as the product is an ectoparasiticide. A second phase environmental risk assessment was provided.

The assessment concluded that deltamethrin would not pose a risk to the environment when used as recommended. It is reported that up to 50% of deltamethrin topically applied to cattle was absorbed through the skin and later excreted almost exclusively in the faeces. In sheep this is thought to be lower. The PEC values for soil, groundwater and surface water were obtained and the product is not expected to pose a risk to the environment when used as directed. Data has been provided on the toxicity of deltamethrin to dung insects and a risk quotient greater than 100 was established. Deltamethrin is also highly toxic to aquatic organisms and honey bees. The following warnings are therefore required:-

- Deltamethrin is toxic to dung insects. The risk to 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 a single treatment per season on the same pasture.
- Deltamethrin has the potential to adversely affect non-target organisms. Following treatment, deltamethrin is excreted in faeces. Deltamethrin excretion may take place over a period of 2 to 4 weeks. Faeces

containing deltamethrin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms.
- Deltamethrin is toxic to aquatic organisms and honey bees.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

Residue depletion studies for meat withdrawal periods were not conducted because the product has been shown to be qualitatively and quantitatively the same as the reference product and the applicant has proposed the same meat withdrawal period for cattle and sheep.

The applicant has provided milk residue depletion studies for cattle and sheep. The study for cattle milk showed the withdrawal period of zero days, already established for the reference product is acceptable. Ewes milk is contraindicated in the reference product, however the applicant submitted a ewes milk residue depletion study that indicated residue levels were below the LOQ from the first collection of milk at zero hours. Therefore a milk withdrawal period of zero hours has also been established for ewes.

The analytical method consisted of protein precipitation with acetonitrile before liquid extraction with tetrabutylmethylether at pH 3. Analysis was performed by reverse phase HPLC with tandem mass spectrometric detection. The method was fully validated.

Withdrawal Periods

Cattle
Meat: 17 days
Milk: Zero hours

Sheep
Meat: 35 days
Milk: Zero hours

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of studies on the tolerance in the target species are not required.

Resistance

The bibliography provided indicates there is resistance to many classes of ectoparasiticides, some of which may be indicated for the treatment of ticks, lice and blowfly. The applicant has provided references that suggest there is resistance to deltamethrin in some species of tick. Adequate warnings and precautions appear on the 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.
- 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.
- The product will reduce the number of flies resting directly on the animal but it is not expected to eliminate all flies on the farm. The strategic use of the product should, therefore, be based on local and regional epidemiological information about the susceptibility of parasites, and used in association with other pest management methods.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application according to Article 13 (3) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of laboratory trials 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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)