Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/ml Oral Solution for Dogs

PuAR correct as of 09/03/2018 when RMS was transferred to FR. Please contact the RMS for future updates

Date Created: 2nd January 2015

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0521/001/DC
Name, strength and pharmaceutical form	Modulis 100 mg/ml Oral Solution for Dogs
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance	Ciclosporin
ATC Vetcode	QL04AD01
Target species	Dogs
Indication for use	Treatment of chronic manifestations of atopic dermatitis in dogs.

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 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	24th September 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This application was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, as a generic application. The reference product was Atopica 50 mg Soft Capsules for Dogs, marketed in the UK since 2003. Suitable bioequivalence studies were performed to show that the different route of presentation of the proposed product and the reference product (capsule versus oral solution), had no effect on relative efficacy. Modulis 100 mg/ml Oral Solution for Dogs does not contain the excipients of the capsule shell of the reference product.

The proposed product contains 100 mg/ml ciclosporin as a microemulsion concentrate, and is indicated for the treatment of chronic atopic dermatitis in dogs. The dose is 5 mg/kg bodyweight per day. Other causes of dermatitis such as ectoparasitic infections, flea or food allergy or bacterial and fungal infections should be ruled out before treatment is started, but it may not be necessary to halt treatment should such infections occur during treatment. The Summary of Product Characteristics (SPC) carries detailed warnings with regard to use of the product. The product is contraindicated in animals with hypersensitivity to the active substance or the excipients, in dogs less than 6 months of age or less than 2 kg in weight, and in animals with a history of malignant disorders or progressive malignant disorders. The SPC additionally carries warnings with regard to the concomitant use of other medicinal products.

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, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[1] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 100 mg/ml ciclosporin and the excipients all-rac-α-tocopherol (E-307), ethanol anhydrous (E-1510), propylene glycol (E-1520), macrogolglycerol hydroxystearate and glycerol monolinoleate.

The container/closure system consists of an amber Type III glass bottle, closed with a child resistant tamper-evident HDPE screw cap, fitted with a transparent LDPE insert, plus a syringe for oral use (transparent natural polypropylene barrel and white HDPE plunger) with a white polypropylene cap. The product is available as follows:

- 5 ml bottle with 1 ml syringe in a cardboard box
- 15 ml bottle with 1 ml syringe in a cardboard box
- 30 ml bottle with 2 ml syringe in a cardboard box
- 50 ml bottle with 2 ml syringe in a cardboard box

Not all product sizes may be marketed.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of antimicrobial preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines. The active substance with excipients is dissolved appropriately and packaged under nitrogen atmosphere under suitable environmental control.

[1] Efficacy – The production of a desired or intended result.

II.C. Control of Starting Materials

The active substance is ciclosporin, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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. Acceptable Certificates of Suitability were submitted. The excipients are appropriately monographed in the Ph. Eur.

II.C.4. Substances of Biological Origin

Scientific data and certificates of suitability have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated. There are no items of animal origin in the product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Tests include those for appearance, density, identification of active substance, purity of product and microbiological quality.

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 3 years was acceptable. Real time and accelerated stability data were provided for the finished product under VICH[2] conditions. No significant adverse effects occurred to the product within the 36 month test period. The conditions for storing the product as specified on the SPC are appropriate.

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

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 30 months.
- Shelf life after first opening the immediate packaging: 3 months.
- Keep the bottle in the outer carton.
- Storage in the refrigerator should be avoided.
- The product contains fat components from natural origin which can become solid at lower temperatures. A jelly-like formation may occur below 20°C which is however reversible at temperatures up to 25°C without affecting the quality of the product.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

As this was a generic application according to Article 13 (1), and bioequivalence with a reference product has been established, results of pharmacological and toxicological tests are not required.

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

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to ciclosporin should avoid contact with the veterinary medicinal product
- Wash hands after administration.
- In the event of accidental contact of product with skin or eyes, the affected area should be washed with clean water.
- In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Environmental Safety

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low, and as a result the assessment for environmental risk ended at Phase I of the VICH decision tree. A Phase II risk assessment was not required. The product is not expected to pose a risk to the environment when used as recommended.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacokinetics

The applicant conducted an *in vivo* bioequivalence study to compare the efficacy of the proposed product with the reference product. As recommended by CVMP[3] guidelines, the two formulations were compared using a single-dose cross-over design, with a two-period, two-sequence testing period. Forty clinically appropriate animals of the same sex, randomised, and taking into account bodyweight and age were tested under fasting conditions. The single dose given equated to approximately 5 mg/kg bodyweight per animal of the proposed product, or one 50 mg capsule of the reference product. A wash-out period of 8 days was provided between treatment periods, and suitable blood tests were performed in order to analyse the amount of ciclosporin in blood plasma.

The extent of exposure to the active substance and the measurement of estimates of peak exposure were reliably measured. Suitable pharmacokinetic statistical analyses were performed by comparing AUC^4_{last} to $AUC_{total,}$ (AUC_{last} was at least 80% of AUC_{total}), and by observing T_{max}[5] and C_{max}[6]. It was found using ANOVA that the 90% confidence interval for determining bioequivalence fell within the acceptance limits of 80 – 125%, thereby demonstrating bioequivalence between the proposed and reference products.

Tolerance in the Target Species

No adverse effects were noted in the bioequivalence study. Additionally, excipients used within the product have been used previously in veterinary medicinal products. No further data were required.

IV.II. Clinical Documentation

As this was a generic application and bioequivalence with a reference product was established, no data were required for this section.

[3] CVMP – Committee for Medicinal Products for Veterinary Use.
[4] AUC – Area under the curve.
[5] T_{max} – Time to maximum active substance concentration.
[6] C_{max} – Maximum concentration of active substance obtained.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable

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MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the 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.

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