ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cyclavance 100 mg/ml Oral Solution for Dogs and Cats

Cyclavance vet 100 mg/ml Oral Solution for Dogs and Cats

(Finland, Norway, Sweden only

Updated: March 2018
(New target species, cats, added to the existing marketing authorisation)

PuAR correct as of 11/10/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0506/001/DC
Name, strength and pharmaceutical form	Cyclavance 100 mg/ml Oral Solution for Dogs and Cats
Applicant	Virbac 1'ere avenue 2065m – LID 06516 Carros Cedex France
Active substance(s)	Ciclosporin
ATC Vetcode	QL04AD01
Target species	Dogs, cats
Indication for use	Treatment of chronic manifestations of atopic dermatitis in dogs. Symptomatic treatment of chronic allergic dermatitis in cats.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23 December 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

Cyclavance 100 mg/ml Oral Solution for Dogs was developed as a generic of Atopica 100 mg Soft Capsules for Dogs, which has been authorised in the UK since October 2003. The proposed product was originally for dogs. Cats were added by way of variation authorisation as a target species in February 2018. Cyclavance is indicated for the treatment of chronic atopic dermatitis in dogs and should be administered orally via the syringe at a dose of 5 mg/kg bodyweight/day. In cats, the product is indicated for the symptomatic treatment of chronic allergic dermatitis, and is administered at 7 mg/kg product/day. Refer to the Summaries of Product Characteristics (SPCs) for full details. The product is contraindicated in dogs less than six months old or less than 2 kg in weight and should not be used in dogs with a history of malignant disorders. Dogs should not be vaccinated with a live vaccine during treatment or within two weeks before or after treatment. Do not use in cats infected with Feline Leukemia Virus (FeLV) or Feline Immunodeficiency Virus (FIV).

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 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 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 the active substance ciclosporin and the excipients all-*rac*-α-tocopherol (E-307), glycerol monolinoleate, ethanol anhydrous (E-1510), macrogolgycerol hydroxystearate and propylene glycol (E-1520).

The container/closure system consists of the following:

Packaging 1:

5 ml bottle, with a dispenser set consisting of a 1 ml PE syringe graduated in increments of 0.05 ml, packaged in a cardboard box.

15 ml bottle, with a dispenser set consisting of a 1 ml PE syringe graduated in increments of 0.05 ml, packaged in a cardboard box.

30 ml bottle, with a dispenser set consisting of a 2 ml PE syringe graduated in increments of 0.1 ml, packaged in a cardboard box.

60 ml bottle, with a dispenser set consisting of a 2 ml PE syringe graduated in increments of 0.1 ml, packaged in a cardboard box.

Packaging 2:

Amber glass (type III) bottles closed with a 20 mm bromobutyl stopper and an aluminum cap with flip-off.

5 ml bottle with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 1 ml polycarbonate syringe graduated in increments of 0.05 ml, packaged in a cardboard box.

15 ml bottle with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 1 ml polycarbonate syringe graduated in increments of 0.05 mL, packaged in a cardboard box.

30 ml bottle, with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 3 ml polypropylene syringe graduated in increments of 0.1 ml, packaged in a cardboard box.

50 ml bottle, with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 3 ml polypropylene syringe graduated in increments of 0.1 ml, packaged in a cardboard box.

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. The product is manufactured by mixing the ethanol, all-*rac*-α-tocopherol and propylene glycol to make a homogenous solution before adding ciclosporin. The macrogolglycerol hydroxystearate and the glycerol monolineate are then mixed with the solution. Finally the solution is filled into bottles which are closed under nitrogen. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is ciclosporin, an established active substance described in the European Pharmacopoeia. Ph. Eur. Certificates of Suitability have been provided for two manufacturers of the active substance. The applicant has provided an in-house specification, in accordance with the Ph. Eur. monograph, for the third 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.

All of the excipients comply with their respective Ph. Eur. monographs and are fully test upon receipt. Certificates of analysis 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 those for identification and assay of the active substance, appearance, density, clarity, purity and microbiological quality.

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. The retest period for the active substance manufactured in accordance with Ph. Eur. Certificates of Suitability is 3 years. The manufacturer of the active substance supported by an in-house specification has not provided stability data. For this manufacturer the applicant has committed to fully test the active substance to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 3 batches of the finished product stored for 6 months at 25°C/60%RH and 40°C/75%RH. Data from photostability and freeze-thaw stability studies were also provided. A shelf life of 2 years is supported.

Data were also provided for the in-use stability of the product. Samples were regularly taken from bottles after broaching. An in-use shelf life of 6 months has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

- The shelf life of the finished product as packaged for sale is 2 years.
- The shelf life after first opening the immediate packaging is 6 months.

Special Precautions for Storage

- Do not refrigerate.
- A jelly-like formation may occur below 15°C which is however reversible at temperatures up to 25°C without affecting the quality of the product.
- After first opening: Do not store above 25°C.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

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 has been demonstrated, results of pharmacological studies are not required. For the

addition of cats to the authorisation, a detailed critical summary and published references were submitted.

Toxicological Studies

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 has been demonstrated, results of toxicological studies are not required. For the addition of cats to the authorisation, a detailed critical summary and published references were submitted.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the most likely routes of exposure are accidental ingestion, dermal exposure by spilling on the skin and subsequent hand to mouth exposure during administration of the product. The product is supplied in child resistant packaging to reduce the risk of exposure. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

> Accidental ingestion of this product may lead to nausea and/or vomiting. To avoid accidental ingestion, the product must be used and kept out of reach of children. Do not leave unattended filled oral syringe in the presence of children. Any uneaten medicated cat food must be disposed of immediately and the bowl washed thoroughly. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician. Ciclosporin can trigger hypersensitivity (allergic) reactions. People with known hypersensitivity to ciclosporin should avoid contact with the product. This product may cause irritation in case of eye contact. Avoid contact with eyes. In case of contact, rinse thoroughly with clean water. Wash hands and any exposed skin after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is for use in non-food producing animals only and risk of exposure to the environment is minimal. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
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 has been demonstrated, pharmacodynamics data are not required.

Pharmacokinetics (Dogs)
An *in vivo* bioequivalence study has been conducted to compare the test and reference products. Forty healthy, male beagle dogs were given a single dose of the test product and the reference product. Twenty dogs in Group 1 received the test product followed by the reference product 8 days later. Group 2 were administered the reference product then the test product 8 days later. The products were administered orally at a dose rate of 5 mg/kg.

Blood samples were collected from the dogs before treatment and at regular intervals up to 48 hours after treatment. Cyclosporin A concentrations were measured in each of the blood samples for comparison between the two products using non-compartmental pharmacokinetic (PK) analysis.
The PK analysis resulted in a mean C_{max}[1] of 772.18 ng/ml (±163.8 SD) for the reference product and 786.97 ng/ml (±188.3 SD) for the test product. The mean AUC_{last}[2] was determined as 3680 ng.h/ml (±1263 SD) and 3728 ng.h/ml (±1243 SD) for the reference and test products respectively.

A ratio of test/reference product C_{max} and AUC_{last} was calculated and the 90% confidence intervals (CI) determined. For C_{max} this resulted in a point estimate of 101.17 (lower CI limit = 96.29, upper CI limit = 106.29). For AUC_{last} the point estimate was 101.43 (lower CI limit = 96.21, upper CI limit = 106.92). The 90% confidence interval for the test/reference product ratio fell within the pre-defined acceptance limits of 80-125%.

The results of this study indicate bioequivalence between the test and reference products. Adverse reactions were also reported when they occurred and similar mild, transient reactions were seen for the test product compared the reference product. This indicates the target species tolerance is similar between the test and reference products. Based on the data provided, bioequivalence has been accepted for the test product and the reference product.

Cats

For the addition of cats to the authorisation in February 2018, the applicant supplied studies available in the public domain. It was considered that the principles of Article 13 (a), (well established veterinary use), as set out in

[1] C_{max} – maximum plasma concentration of active substance
[2] AUC – Area under the curve

Directive 2009/9/EC applied. Studies submitted on a human reference product, Neoral, alongside Atopica 100 mg/ml oral solution for cats were considered appropriate in order to permit cats to be added as a target species to the marketing authorisation.

Tolerance in the Target Species of Animals

Dogs
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 has been demonstrated, results of tolerance studies are not required.

Cats
A series of published tolerance studies were submitted for a variation to the marketing authorisation, by which cats were added to the product indication as a target species.

IV.B Clinical Studies

Laboratory Trials

Dogs
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 has been demonstrated, results of laboratory trials are not required.

Cats

A series of published studies were submitted for a variation to the marketing authorisation, by which cats were added to the product indication as a target species.

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)