MINISTERIO
DE SANIDAD, CONSUMO
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agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

TRIDERM CUTANEOUS SPRAY SOLUTION FOR DOGS

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0287/001/ DC
Name, strength and pharmaceutical form	Triderm cutaneous spray solution for dogs
Applicant	Organit Kft., Homoksor 7., Székesfehérvár, H-8000, Hungary.
Active substance(s)	Marbofloxacin Ketoconazole Prednisolone
ATC Vet code	QD06C
Target species	Dogs
Indication for use	Treatment of acute dermatitis when mixed infection caused by *Pseudomonas aeruginos*a or *Staphylococcus pseudintermedius* susceptible to marbofloxacin and *Malassezia pachydermatis* susceptible to ketoconazole is demonstrated. The veterinary medicinal product should be used based on susceptibility testing on the bacteria isolated from the animal.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Article 12(3) of Directive 2001/82/EC, amended by Directive 2004/28/EC
Date of completion of the original decentralised procedure	6th February 2019
Date product first authorised in the Reference Member State (MRP only)	NA
Concerned Member States for original procedure	CY, EL, LT, LV, MT, PL and PT

I. SCIENTIFIC OVERVIEW

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 specie; the slight 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains marbofloxacin (1.025 mg/ml), ketoconazole (2.041 mg/ml) and prednisolone (0.926 mg/ml) as active substances. Other ingredients are dimethyl sulfoxide, polysorbate 80, propylene glycol, ethanol (96%) and water for injection.

The container/closure system is a 30 ml polyethylene terephthalate (PET) bottle with a spraying pump in a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the 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

All active substances are described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substances specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications have been provided.

Scientific data and certificate of suitability (CEP) issued by the EDQM have been provided for the active substances prednisolone and ketoconazole. For marbofloxacin, the information is provided according to the Active Substance Master File (ASMF) procedure. The provided information is considered appropriate.

Satisfactory TSE information has been provided in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

D. Control on intermediate products

Not applicable.

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.

F. Stability

Stability data on the active substances, marbofloxacin and ketoconazole, have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. For prednisolone, a retest period is included in the certificate of suitability issued by the EDQM.

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 (2 years) when stored under the approved conditions.

Appropriate data have been provided to support the in-use shelf-life of the product.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that:

Marbofloxacin has a rapid, concentration dependent bactericidal activiity. Topoisomerase II is the major target of fluoroquinolone antibacterial agents in Gram-negative bacteria whereas topoisomerase IV may be the primary target in Gram-positive bacteria.

Ketoconazole at usual doses and serum concentrations is fungistatic against susceptible fungi. At higher concentrations for prolonged periods of time or against very susceptible organisms, this agent may be fungicidal. Antifungal action is the inhibition of ergosterol synthesis.

Prednisolone is a synthetic corticosteroid that inhibits the synthesis of eicosanoid molecules during the inflammatory processes due to the inhibition of phospholipase A2 enzyme. It demonstrates pronounced local and systemic anti-inflamatory properties.

The applicant has also provided bibliographical data which show that marbofloxacin and ketoconazole can be absorbed systemically only at low proportion, and prednisolone may be absorbed slowly but completely.

Toxicological Studies

The applicant has provided bibliographical data which show that:

- Single Dose Toxicity

Marbofloxacin has a low acute toxicity. Local and systemic acute toxic effects after dermal absorption in animals have not been reported.
Acute oral LD50: 1781 mg/kg bw (male ICR mice) - 3772 mg/kg bw (female Sprague Dawley rats).
Acute subcutaneous LD50: 972 mg/kg bw (female ICR mice) - 2094 mg/kg bw (male Wistar rats).
The signs of toxicity included decreased activity, tremors and convulsions. The substance was only a mild skin and eye irritant.

Ketoconazole has relatively low toxicity. The toxic effects are liver dysfunction, behavioral changes and coma. Local and systemic acute toxic effects after dermal absorption in animals have not been reported yet.
Acute oral LD50: 166 mg/kg bw (rats) - 618 mg/kg (mouse)
Acute intravenous LD50: 23.3 mg/kg (dogs and guinea pigs) - 86 mg/kg bw (rats)
Acute intraperitoneal LD50: 1474 mg/kg (rat) - 2937 mg/kg (ip)
Acute subcutaneous LD50: >2400 mg/kg (rat) - >4000 mg/kg (mouse)

Prednisolone has relatively low acute toxicity. The toxic effects are behavioural changes and psychosis. Local and systemic acute toxic effects after dermal absorption in animals have not been reported yet.
Acute oral LD50: 1680 mg/kg bw (male and female Swiss mice)
Acute subcutaneous LD50: 147 mg/kg bw (female Sherman rats)
Acute intraperitoneal LD50: 767 mg/kg bw (mice).

- Repeated Dose Toxicity

Marbofloxacin: the lowest NOEL of 4 mg/kg bw/day was established in a 13-week repeat-dose study in rats by oral route at doses of 0, 4, 50 and 600 mg/kg bw/day. The same NOEL was established in a 13-week study in adult dogs treated daily with oral doses of 1, 4,or 40 mg marbofloxacin/kg bw.

Ketoconazole: in dogs treated with ketoconazole, the most common adverse effects were inappetence, pruritus, alopecia and reversible lightening of the hair, and long-term treatment of dogs has been associated with development of cataracts. The lowest NOAEL of 10 mg/kg bw for maternal and foetal toxicity was established from a study in rats (oral exposure for 3 weeks). Chronic exposure of ketoconazole orally to rats for 6 months at 5 mg/kg bw showed no adverse effects.

Prednisolone: studies in mice, rabbits, hamster and rats showed that prednisolone caused malformations including draft palate when administered orally. A NOEL of 3 mg/kg bw/day in rats was established (maternotoxicity and foetotoxicity).

- Reproductive Toxicity, including Teratogenicity:

Large doses of marbofloxacin can cause foetotoxicity effects. The lowest foetotoxicity NOEL was 10 mg/kg bw/day from a 2-generation study in rats.

Ketoconazole can inhibit the fertility in both male and female animals at high doses, as shown in studies in rats and mice.

Prednisolone: studies in mice, rabbits, hamsters and rats showed that prednisolone caused malformations including draft palate when administered parenterally.

- Mutagenicity

Marbofloxacin, prednisone and ketoconazole are not genotoxic.

- Carcinogenicity:

No evidence of carcinogenicity was found for marbofloxacin, ketoconazole and prednisolone.

Other Studies

The applicant has not presented additional studies of dermal and eye irritation or skin sensitization with the final formulation. The components of the VMP can produce skin and eye irritation, as well as sensitization reactions.

Observations in Humans

Marbofloxacin is not authorised for human beings, but similar molecules are used in human medicine. The fluoroquinolones applied in human beings are relatively safe and well tolerated agents.

Ketoconazole: the most common adverse effects of ketoconazole in humans are nausea, vomiting, dizziness, itching and increases in liver enzyme levels. After topical administration of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Prednisolone: preparations containing prednisolone are available for oral, intra-articular, intramuscular and topical administration in humans. Daily oral doses of up to 10 mg/person are well tolerated, but the risk of adverse effects increases above that dose level. Growth retardation may occur in children receiving long-term oral treatment.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main route of exposure is the accidental ingestion by a child, and also dermal and eye exposure. The product can produce an eye and skin irritation, as well as it can cause allergic reactions too.

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

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the product will only be used in non-food animals.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

A review of the literature was made, and the applicant provided and summarized bibliographic references that explain the mechanism of action. The applicant has provided several scientific publications regarding bacteria (*S. pseudointermedius* and *P. aeruginosa*) and yeast (*M. pachydermatis*) coinfection occurring in dermatitis. In addition, the inhibition of the inflammation with prednisolone in pyotraumatic dermatitis is also recommended. Potential advantages of fixed combinations include facilitating animal handling as well as owner's compliance when simultaneous administration of more than one pharmacologically active substance is justified for therapeutically reasons. In this sense, the combination is considered appropriated.

Studies were carried out by the applicant to determine MIC_{90}, and MBC values of bacteria and fungi isolated from dermatitis cases.
Pharmacokinetic data were obtained from the tolerance study, and validation of the method used was sent and considered adequate.

Tolerance in the Target Species of Animals

Two tolerance studies were performed: one using the proposed route of administration and the other one assaying the oral route, in case of a possible ingestion.

Resistance

The applicant has provided two MIC data studies from 2017 and 2018. These results show that the resistance levels to marbofloxacin and ketoconazole have not increased over the last 7-8 years at least in the regions tested.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory trials

The selection of dose of prednisolone is based on dermatological and other topical (conjunctival, outer ear) products in which the inclusion rate of this glucocorticoid is 0.1-0.5%, depending on the salt form. For marbofloxacin, the dose agrees with the minimum 10 C_{max}/MIC ratio of all investigated bacteria (MIC_{100}). Finally, the dose of ketoconazole reveals that the concentrations reached are adequate for a twice-daily administration taking into account the AUC_{12h} of the product, which contains 2000 µg/ml of ketoconazole. The applicant showed no interaction between the pharmacologically active substances.

Field Trials

One field trial performed under GCP and comparing with a similar control product, confirmed the clinical efficacy. *P. aeruginosa* or *S. pseudointermedius* together with *M. pachydermatis* infections were confirmed at the beginning of the study for all dogs (n=40). Microbiological samples were collected from each dog, at day 0 and 7 and/or 14 according to the study protocol. The duration of the treatment was 7 or 14 days depending on the clinical score on day 7. 36 and 4 dogs reduced their score to 0 and 1 respectively either on day 7 or 14. That is, all the animals were clinically cured at day 14. Also, the laboratory microbiological results were negative in all the cases in which the dermatitis score was reduced to 1 or 0. The microbiological samples from day 7 are available around day 10 for bacteria and day 13 for yeast. Taking into account this and that all the animals from the study that received the 14 day treatment were healed, it can be justified to extent the treatment to 14 days in case the infection still present at day 7. If the animal is not healed at day 14, it is recommended to change the treatment. Adequate warnings and precautions appear on the product literature.

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 risk benefit 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 veterinary Heads of Agencies website (www.hma.eu).

This section 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.

None