DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GEFRIDERM cutaneous spray solution for dogs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0371/001/DC
Name, strength and pharmaceutical form	GEFRIDERM cutaneous spray solution for dogs
Applicant	Alpha-Vet Veterinary Ltd., Hofherr A. str. 42, Budapest, H-1194, Hungary
Active substance(s)	Marbofloxacin Ketoconazole Prednisolone
ATC Vetcode	QD07CA03
Target species	Dogs
Indication for use	Treatment of acute superficial dermatitis caused by mixed infections with Pseudomonas aeruginosa or Staphylococcus pseudintermedius susceptible to marbofloxacin and Malassezia pachydermatis susceptible to ketoconazole. The indication is limited to focal skin infections (e.g. hot spots, intertrigo, superficial folliculitis).

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	Decentralised application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original <mutual recognition><decentralised>procedure	21/10/2020
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	DE; EE; IE; UK

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 species.
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, ketoconazole and prednisolone as active substances and dimetilsulfoxide, polysorbate 80, propylene glycol, ethanol (96%) and water for injections as excipients.

The container closure system is box with 1 PET (polyethylene terephthalate) bottle of 30 ml closed with a spraying pump. The materials of the pump are polyethylene, polypropylene, solvent resistant thermoplastic elastomer, polyoxymethylene and stainless steel.

The choice of the formulation has been 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

The active substances are marbofloxacin, prednisolone and ketoconazole, an established active substances 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 material. Batch analytical data demonstrating compliance with these specifications have been provided.

Scientific data (ASMF for Marbofloxacin) and certificates of suitability issued by the EDQM (for Ketoconazole and Prednisolone) 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 confirmed.

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

Either stability data on the active substances have been provided in accordance with applicable European guidelines or the re-test period is included in the currently valid CEP.

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 (4 years) when stored under the approved conditions (Do not refrigerate or freeze).

Current shelf life after the first opening of the product (28 days) has been supported by relevant stability data in line with relevant European guidelines.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which shows 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 shows 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). NOEL of 20 µg/kg b.w./day was established for induction of tyrosine aminotransferase activity study in rats.

- 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 (if necessary):

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

Other Studies

The applicant has not presented additional studies of dermal 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

The applicant has provided bibliographical information which shows that:

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 may cause eye and skin irritation, as well as allergic reactions. Excessive exposure to the product may lead to foetal defects, or reduced sperm viability.

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(pharmaceuticals only)

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.

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.

Tolerance in the Target Species of Animals

Two tolerance studies (1 and 2) were performed: one using the proposed route of administration and the other one assaying the oral route, in case of a possible ingestion.

1. The aim of this study was to obtain information on the local and possible general toxicity of the product and on plasma levels of the active components, marbofloxacin, ketoconazole and prednisolon in Beagle dogs administered locally (skin) twice daily over a period of 14 days at 4 dose levels (control: sterile isotonic saline solution; intended therapeutic dose, 3 and 5 fold of the intended therapeutic dose). To assess the reversibility of any effect a 7-day period of observation was applied. Blood samples were collected for HPLC determination of plasma levels of the active components to provide information on the systemic exposure.
All groups consisted of 4 male and 4 female animals. Treatment was applied on the skin on the left side of the neck.
Conclusion: based on the results of this study, it can be concluded, that the product administered topically onto the skin twice a day, one area per dog, over a 14-day period in 3 and 5 fold of the intended therapeutic dose was well tolerated.

2. The purpose of this study was to obtain information on the general toxicity of the product in Beagle dogs administered orally twice daily over a period of 14 days with the therapeutic dose of the intended administration route. to assess the reversibility of any effect a 7-day period of observation was applied. Oral administration was applied for the demonstration of any adverse effect after the possible accidental oral ingestion

during therapeutic usage (therapeutic dose was applied to 4 male and 4 female animals, and control group was also included).
Conclusion: based on the results of this study, it can be concluded, that the product administered orally in the intended therapeutic dose twice a day over a 14-day period was well tolerated.

Resistance

Two MIC data studies from 2017 and 2018 were provided. 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

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_{90}). According to this approach, which takes into account biofilm formation factor, the minimum recommended concentration of marbofloxacin would be 840 µg/ml. The marbofloxacin concentration for the final formulation is 1 025 µg/ml. 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. Mixed infections were confirmed at the beginning of the study. 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. All 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. If the animal is not healed at day 14, it is recommended to change the treatment.
The analysis was performed performed for the primary endpoint taking into account the 56 eligible animals, using a two-sided 5% level of significance and with a non-inferiority of -0.15. All the statistical methods showed that the lower limit of the 95% confidence limit exceeded the chosen -0.15 limit. Therefore, considering these criteria the non-inferiority of the tested product compared to the control was demonstrated. According to what has been demonstrated in the clinical trial, the indication has been set to the treatment of acute superficial dermatitis caused by mixed infections with *Pseudomonas aeruginos*a or *Staphylococcus pseudintermedius* susceptible to marbofloxacin and

Malassezia pachydermatis susceptible to ketoconazole. The indication is limited to focal skin infections (e.g. hot spots, intertrigo, superficial folliculitis).
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.

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