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

Actimarbo 5 mg Flavoured Tablets for Dogs and Cats
Actimarbo 20 mg Flavoured Tablets for Dogs
Actimarbo 80 mg Flavoured Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0461/001-3/DC
Name, strength and pharmaceutical form	Actimarbo 5 mg Flavoured Tablets for Dogs and Cats Actimarbo 20 mg Flavoured Tablets for Dogs Actimarbo 80 mg Flavoured Tablets for Dogs
Applicant	Ecuphar NV Legeweg 157-i 8020 Oostkamp Belgium
Active substance(s)	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Dogs, cats (5 mg only)
Indication for use	Dogs: Skin and soft tissue infections caused by susceptible strains of organisms. Urinary tract infections (UTI) associated or not with prostatitis or epididymitis caused by susceptible strains of organisms. Respiratory infections, caused by susceptible strains of organisms. Cats: Marbofloxacin is indicated in the treatment of skin and soft tissue infections (wounds, abscesses, phlegmons) and upper respiratory tract infections caused by susceptible strains of organisms.

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	26th June 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Czech Republic, France, Germany, Italy, Netherlands, Portugal, Slovakia, Spain.

I. SCIENTIFIC OVERVIEW

Actimarbo Flavoured Tablets have been developed as generic products in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference products were Marbocyl P5 Tablets, Marbocyl P20 Tablets and Marbocyl P 80mg Tablets, first authorised in the UK in February 1995. The product contains the active substance marbofloxacin, which belongs to the fluoroquniolone group of antibacterials.

The products are indicated in the treatment of skin and soft tissue infections, urinary tract infections and respiratory tract infections in cats and dogs. The product is contraindicated in dogs less than 12 months and cats less than 16 weeks, animals with a known hypersensitivity to fluoroquinolones and in cases of confirmed of suspected resistance to fluoroquinolones. Actimarbo should be administered at a dose rate of 2 mg/kg once daily.

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, 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.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains marbofloxacin as active substance and lactose monohydrate, cellulose microcrystalline, povidone K90, purified water, crospovidone, meat flavour, silica (colloidal anhydrous) and magnesium stearate as excipients.

The container/closure system consists of a blister pack containing 10 tablets (5 mg and 20 mg) or 6 tablets (80 mg). The blister is made of OPA/Alu/PVC base, heat sealed with aluminium foil lid and packaged in a cardboard carton. The 5mg and 20 mg products are available in pack sizes of 10, 20 or 100 tablets and the 80 mg product is available in pack sizes of 6, 12 or 72 tablets. 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 two batches of the product have been presented in accordance with the relevant European guidelines. The product is manufactured firstly by sifting the ingredients. Dry mixing of the marbofloxacin with lactose monohydrate and cellulose microcrystalline occurs before addition of the povidone K90 and purified water for granulation. Following drying and sizing, the remaining excipients are blended with the substance, the mixture compressed into tablet form and packaged into the blister strips.

C. Control of Starting Materials

The active substance is marbofloxacin, an established active substance described in the European Pharmacopoeia (Ph. Eur). Data on the active substance is supplied in the form of an active substance master file (ASMF). 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 excipients comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

This product contains lactose sourced from milk that is fit for human consumption. Scientific data and certificates of suitability issued by the EDQM 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.

E. Control on intermediate products

During manufacture granules are formed prior to compression into tablets. The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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 test on the product include the identification and assay of the active substance, identification of impurities, tests for hardness of the tablets, weight of the tablets and microbial purity.

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.

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 5 years is supported.

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. Long-term, intermediate and accelerated studies were performed where the product was stored at 25ºC for 48 months, 30ºC for 12 months and 40ºC for 6 months. A shelf life of 3 years has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale is 3 years.

- Shelf life of halved tablets is 7 days.
- In case of using half tablets: Return any remaining half tablet to the opened blister pocket. Use the remaining half tablet for the next administration.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics
Marbofloxacin is a synthetic antibacterial agent belonging to the fluoroquinolone group. Marbofloxacin has broad spectrum activity and acts by impairing DNA replication through inhibition of DNA gyrase. Due to the higher affinity of marbofloxacin to bacterial enzymes than mammalian enzymes, adverse effects are reduced but rapid bactericidal activity occurs.

Marbofloxacin is effective against a wide range of Gram-positive bacteria. In vitro activity against a several canine and feline pathogens is good. Strains with MIC ≤ 1 µg/ml are sensitive to marbofloxacin whereas strains with MIC ≥ 4 µg/ml are resistant.

Pharmacokinetics
Marbofloxacin is readily absorbed following oral administration. When administered to dogs and cats at the recommended dose of 2 mg/kg, maximum plasma concentrations of 1.5 µg/ml is reached within 2 hours. The bioavailability of marbofloxacin is close to 100%.

Marbofloxacin is binds weakly to plasma proteins (<10%) and is extensively distributed in most tissues, including liver, kidney, skin, lung, bladder and digestive tract. A higher concentration of marbofloxacin is normally observed in the tissues than in plasma. Marbofloxacin is eliminated slowly due to the long half life, 14 hours in dogs and 10 hours in cats. Marbofloxacin is predominantly eliminated unchanged in urine and faeces.

Toxicological Studies

The applicant has provided a review of some published studies concerning the toxicology of marbofloxacin.

- Single Dose Toxicity
  Studies of marbofloxacin in mice and rats have determined and LD_{50} of 887.8 – 1781 mg/kg in mice and 3772 mg/kg in rats. The observed signs of toxicity included decreased activity, tremors and convulsions.

- Repeated Dose Toxicity
  In one study marbofloxacin was orally administered to mice at a doses up to 178 mg/kg bw for 30 days. No mice died and there were no significant differences in bodyweight. A NOEL[2] was not established.

  A 13 week repeat dose study on rats was included. Rats received marbofloxacin at doses of 0, 4, 50 and 600 mg/kg bw/day administered via the oral route. A NOEL of 0.4 mg kg bw/day was established. The higher doses had a toxic effect on the male reproductive organs and induced arthropathy.

  Repeat dose studies in dogs were also included by the applicant. In one study dogs were given marbofloxacin orally at dose rates of 1, 4 and 40 mg/kg bw/day for 13 weeks. A NOEL of 4 mg/kg bw/day was established. Adverse effects observed included typical quinolone-induced changes to the articular cartilage in dogs receiving the highest dose rate.

- Reproductive Toxicity, including Teratogenicity
  Rats were given marbofloxacin at doses of 10, 70 or 500 mg/kg bw/day. Those receiving the highest dose exhibited signs of toxicity and male fertility was impaired. At 500 mg/kg bw reduced implantation rate, pup weight and litter size were observed as well as increased pup mortality. A NOEL of 10 mg/kg bw/day was determined.

  Foetotoxicity was investigated in a study where pregnant rabbits received 10, 30 or 80 mg/kg bw of marbofloxacin orally per day on day 6-18 of gestation. A similar study in rats saw marbofloxacin administered orally on day 6-15 of gestation at doses of 10, 85 or 700 mg/kg bw/day. There was no evidence of teratogenicity at any dose for both rats and rabbits. The NOEL for foetotoxicity in rabbits was 30 mg/kg bw/day and in rats was 85 mg/kg bw/day. The NOEL for maternal toxicity was established as 10 mg/kg bw/day.

- Mutagenicity
  Sperm abnormality and bone marrow micronucleus tests performed in mice produced negative results, indicating marbofloxacin is non-mutagenic. Further *in vivo* studies, including a UDS assay in rat liver, were performed and produced negative results. It was concluded that marbofloxacin is not mutagenic.

[2] NOEL – No observable effect limit

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which considered the most likely routes of exposure to be dermal through handling the tablets or accidental ingestion. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to (fluoro)quinolones should avoid contact with the veterinary medicinal product.
- In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands 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 active substance, marbofloxacin, is well known and as the product is only for use in cats and dogs the risk posed to the environment is low. 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
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Tolerance in the Target Species of Animals

As this is a generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product can be assumed tolerance studies in the target species are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

The applicant has provided information on resistance to marbofloxacin. One study submitted by the applicant looked at isolated *Staphylococcus intermedius* strains originating from dogs. *In vitro* antimicrobial susceptibility testing was performed and 98% of the strains were identified as being sensitive to marbofloxacin.

Resistance to marbofloxacin has been observed in *Streptococcus* and marbofloxacin is not active against anaerobes, yeast or fungi. Resistance to fluoroquinolones is thought to occur via chromosomal mutation with 3 mechanisms. These are decrease of bacterial wall permeability, expression of an efflux pump or mutation of enzymes for molecule binding. There is no evidence of any significant development, evolution or spread of resistance in pathogens isolated in companion animals since marbofloxacin has been used by veterinarians.

Suitable warnings are included on the SPC and product literature:

- Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly to other classes of antimicrobials. Whenever possible, use of fluoroquinolones should be based on susceptibility testing. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease effectiveness of treatment with other quinolones due to the potential for cross-resistance.

IV.B Clinical Studies

This is a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product is claimed. The applicant has not submitted bioequivalence studies but provided dissolution studies to demonstrate the test and reference product are the same. The results of these studies fulfil the dissolution biowaiver and

therefore results of clinical studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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.

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