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

Marfloxin 5 mg Tablets for Cats and Dogs
Marfloxin 20 mg Tablets for Dogs
Marfloxin 80 mg Tablets for Dogs (AT, BE, BG, EE, DE, FR, IE, IT, GR, NL, PL, PT, RO, SI, ES, UK)

Quiflox vet 5mg Tablets for Cats and Dogs
Quiflox vet 20 mg Tablets for Dogs
Quiflox vet 80 mg Tablets for Dogs (CZ, HU, LT, LV, SK)

Quiflox 5 mg Tablets for Cats and Dogs
Quiflox 20 mg Tablets for Dogs
Quiflox 80 mg Tablets for Dogs (NO, SE, FI)

Marbiflox 5 mg Tablets for Cats and Dogs
Marbiflox 20 mg Tablets for Dogs
Marbiflox 80 mg Tablets for Dogs (DK)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0430/001/DC UK/V/0430/002/DC UK/V/0430/003/DC
Name, strength and pharmaceutical form	Marfloxin 5 mg Tablets for Cats and Dogs Marfloxin 20 mg Tablets for Dogs Marfloxin 80 mg Tablets for Dogs
Applicant	KRKA, D.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Cats and/or dogs
Indication for use	Treatment of infections caused by strains of microorganisms susceptible to marbofloxacin. Dogs – skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis, cellulitis); – urinary tract infections (UTI) associated or not with prostatitis or epididymitis; – respiratory tract infections. Cats – skin and soft tissue infections (wounds, abscesses, phlegmons); – upper respiratory tract infections.

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	21st November 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	**UK/V/0430/001 – 003/DC** Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

These products were the subject of generic applications, in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference products were Marbocyl P5 Tablets, Marbocyl P20 Tablets and Marbocyl P80 Tablets, marketed in the UK since June 2003. Marbocyl 5 mg Tablets, Marbocyl 20 mg Tablets and Marbocyl 80 mg Tablets are part of a global marketing authorisation authorised in the UK in February 1995. Where the product may be used in dogs, the indication is for the treatment of skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis, and cellulitis), in addition to urinary tract infections (UTI) associated or not with prostatitis or epididymitis, and respiratory tract infections. In cats, the products may be used to treat skin and soft tissue infections (wounds, abscesses, phlegmons), and upper respiratory tract infections.

The products are 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 at 5 mg, 20 mg or 80 mg and the excipients lactose monohydrate, povidone (K90), yeast powder, meat flavour, crospovidone, castor oil hydrogenated, silica colloidal anhydrous and magnesium stearate.

The container/closure system consists of a polyvinylchloride-aluminium-oriented polyamide/aluminium cold formed blister containing 10 tablets. Boxes are provided with the instruction leaflet containing 10 tablets or 100 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The process consists of the mixing of active substance and excipients, followed by sieving granulation and drying processes, and subsequent compression of tablets.

C. Control of Starting Materials

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.

The active substance is marbofloxacin, 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. Of the excipients, only meat flavour and yeast powder are not monographed in the Ph Eur. Suitable specifications were provided.

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

Suitable data were provided. Lactose used as an excipient is sourced from milk which is fit for human consumption.

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. 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 on the finished product include those relevant for the dosage form.

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 two years was established. For the finished product, suitable stability studies showed that the product was stable under conditions as described in the SPC.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
- Shelf life of half-tablets: 5 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, 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 Testing

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which addressed toxicity of the active substance, dermal, oral and ocular exposure, risk management and assessment of risk. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the product is only to be given to cats and dogs, no further assessment was required. 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

No new data were submitted for pharmacodynamic parameters. An *in vivo* bioequivalence study was provided, which was performed using 80 mg test and reference (Marbocyl P80 Tablets) products. This was a GLP[2]-compliant randomised, two-treatment, two-sequence, single dose cross-over study, under fasting conditions, with a thirteen day washout period between the two treatments. A suitable number of male animals were used for each treatment group, with a single dose of one tablet being given orally, equivalent to 5 mg/kg as an upper limit. The recommended dose is 2 mg/kg. Blood samples were collected at various time points. No serious treatment-related adverse events were reported, and suitable statistical analyses were performed on relevant AUC[3] and C_{max}[4] and T_{max}[5] parameters. It was concluded from 90% confidence limit data that bioequivalence had been established. A supporting bibliographical reference was also provided

In vitro dissolution studies were performed in order to extrapolate results obtained from the 80 mg bioequivalence study. These provided acceptable data permitting bioequivalence to be accepted for the 5 mg and 20 mg strengths.

[2] GLP – Good Laboratory Practise.
[3] AUC – Area under the curve.
[4] C_{max} – Maximum plasma concentration of active substance.
[5] T_{max} – Time at which the active substance meets maximal concentration.

Tolerance in the Target Species of Animals

No specific tolerances studies were required, as the products exhibited bioequivalence with the reference products. However, during the bioequivalence study, the product was administered at approximately 4.5 mg/kg, which was higher than the recommended dose of 2.5 mg/kg. No serious treatment-related adverse events were noted.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The products possess the same qualitative and quantitative formulation as the reference products, therefore the same warnings and precautions apply to all the products. Suitable warnings are cited in the SPC. Eight published literature references supported this section of the dossier.

IV.B Clinical Studies

Laboratory Trials

As these were generic applications, and bioequivalence was established with reference products, no data were required for this section.

Field Trials

As these were generic applications, and bioequivalence was established with reference products, no data were required for this section.

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 Heads of Medicines Agencies (veterinary) (HMA(v)) 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