ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES

United Kingdom
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Marbotab P 80 mg Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0431/002/DC
Name, strength and pharmaceutical form	Marbotab P 80mg Tablets for Dogs
Applicant	CP Pharma Handelsgesellschaft mbH, Ostlandring 13, 31303 Burgdorf, Germany
Active substance(s)	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Dogs
Indication for use	**In dogs:** • Skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis, cellulitis); • Urinary tract infections (UTI) associated or not with prostatitis; • Respiratory tract infections.

MODULE 2

The Summary of Product Characteristics (SPC) for these products 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 December 2012.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Italy, Belgium, Spain, Poland, France, Hungary, Germany, Ireland, Denmark and The Netherlands.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted under Article 13 (1) of Directive 2001/82/EC, as amended. The reference product was Marbocyl P80 Tablet. The product is intended for use to treat infections caused by microorganisms susceptible to marbofloxacin. In dogs, the product is intended to treat skin and soft tissue infections, urinary tract infections and respiratory tract infections.

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 products 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 (20 mg per tablet) and lactose monohydrate, powdered cellulose, crospovidone, colloidal anhydrous silica, calcium behenate, deactivated yeast and artificial beef flavour (PC-0125) as excipients.

The container/closure system consists of aluminium-polyamide/aluminium/polyvinyl chloride blisters containing 10 tablets in a carton box. Blister packs are available in cartons of 20, 50, 100 or 200 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and 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 in accordance with the European Pharmacopoeia and relevant European guidelines.

The method consists of three stages of mixing during which all ingredients are added. The resulting mixture is then dried and compressed. In process controls are performed at the end of the mixing, with colour, loss on drying and bulk density examples of parameters. Additional tests are performed after tabletting, during which size, fragility and appearance are analysed.

C. Control of Starting Materials

The active substance is marbofloxacin, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice (GMP), and the active substance specification is considered adequate to control the quality of the material. Batch analytical data from three batches demonstrating compliance with this specification have been provided along with an Active Substance Master File (ASMF).

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

Substances of animal origin consist of lactose and some porcine materials. Lactose is sourced from milk fir for human consumption and the artificial beef flavour used contains no ingredients of bovine, ovine and/or caprine origin. A suitable table describing data related to transmissible spongiform encephalopathies was provided.

E. Control on intermediate products

The applicant provided a specification for tests to be performed during production.

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 products. 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. Tests include those for appearance, tablet diameter, weight, divisibility, friability, loss on drying, dissolution, identity, impurities and microbiological content.

G. Stability

Stability data on the active substance and finished product was provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary products as packaged for sale: 2 years.
Shelf life of quartered tablets: 72 hours.

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. The product and reference product differ with regard to excipients.

User Safety

The applicant has provided a user risk assessment in compliance with the relevant guideline which shows that the risks to the user from use of these products are no greater than from use of the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician. Wear gloves when handling or dividing tablets. Wash hands after use.

- People with known hypersensitivity to fluoroquinolones should avoid using this product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the assessment stops at Phase I because the product is for use in dogs only and environmental exposure will not be extensive. 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

As this is a generic application according to Article 13, and bioequivalence with a reference product was demonstrated via two submitted GLP-controlled bioequivalence studies, further efficacy studies were not required. The efficacy claims for these products are equivalent to those of the reference product.

Pharmacokinetics

Bioequivalence studies

The first study was performed in dogs using Marbotab P 20 mg and the reference product Marbocyl P 20 mg. A suitable number of animals were used in a single-dose, randomised, two-period, two-treatment, two-sequence cross over study, with a washout period of 7 days. Animals were randomised to 2 groups of 12 replicates of 2 animals, and ranked by bodyweight within gender. The products were administered as a single oral dose of half tablets per animal, given equivalent to 10 mg marbofloxacin per 5 kg bodyweight per animal. Intended dose was 2 mg/kg/ bodyweight.

Samples were taken at various time points, according to pharmacokinetic parameters examined, and animals were observed for adverse reactions. Parameters used for pharmacokinetic analysis and subsequent statistical analysis were C_{max}, T_{max}, K_{el}, $T_{1/2,}$ $AUC_{0-t,}$ $AUC_{extrapolated,}$ $AUC_{total,}$ % $AUC_{extrapolated}$, $AUMC_{0-t,}$ $AUMC_{extra,}$ $AUMC_{total}$, %$AUMC_{extra}$, and MRT, $F_{relative.}$ Pivotal parameters were AUC_{0-t} and $C_{max.}$ A confidence interval of 90% was defined for the pivotal parameters, and this was achieved as the two treatments feel within the specified 0.80 – 1.25 range.

A second study was performed in cats, using the proposed 20 mg Marbotab product and the Marbocyl 20 mg reference product. This was a single-dose, randomised, two-period, two-treatment, two-sequence cross over study, with a washout period of 14 days. Animals of both gender were randomised to 2 groups of 12 animals per group. Half tablets were given as appropriate in order to obtain a dose rate of 2 mg/kg/bodyweight.

Samples were taken at various time points, according to pharmacokinetic parameters examined, and animals were observed for adverse reactions. Parameters used for pharmacokinetic analysis and subsequent statistical analysis were C_{max}, T_{max}, K_{el}, $T_{1/2,}$ $AUC_{0-t,}$ $AUC_{extrapolated,}$ $AUC_{total,}$ % $AUC_{extrapolated}$, $AUMC_{0-t,}$ $AUMC_{extra,}$ $AUMC_{total}$, %$AUMC_{extra}$, and MRT, $F_{relative.}$ Pivotal parameters Were AUC_{0-t}[2] and C_{max}[3]. A confidence interval of 90% was defined for the pivotal parameters, and this was achieved as the two treatments fell within the specified 0.80 – 1.25 range.

A biowaiver was permitted in order to extrapolate the results obtained using the 20 mg tablet for use of the 80 mg tablet. This was allowed via use of suitable dissolution studies.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, tolerance studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, resistance 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 products are 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 products for humans and the environment is acceptable.

[2] AUC – Area under the time versus concentration curve.
[3] C_{max} – Maximum plasma concentration of active susbstance.

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)