Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Efex 10 mg Chewable Tablets for Cats and Dogs
Efex vet 10 mg chewable tablets for cats and dogs (FI)
Axor 10 mg chewable tablets for cats and dogs (DK)

Efex 40 mg Chewable Tablets for Dogs
Efex Vet 40 mg Chewable Tablets for Dogs (FI)
Axor 40 mg chewable tablets for dogs (DK)

Efex 100 mg Chewable Tablets for Dogs
Efex vet 100 mg chewable tablets for dogs (FI)
Axor 100 mg chewable tablets for dogs (DK)

PuAR correct as of 09/11/2018 when RMS was transferred to FR.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0441/001/DC UK/V/0441/002/DC UK/V/0441/003/DC
Name, strength and pharmaceutical form	Efex 10 mg Chewable Tablets for Cats and Dogs Efex 40 mg Chewable Tablets for Dogs Efex 100 mg Chewable Tablets for Dogs
Applicant	SOGEVAL 200 avenue de Mayenne Zone Industrielle des Touches 53000 LAVAL FRANCE
Active substance	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Dogs, Dogs and Cats

Indication for use	Efex 10 mg Chewable Tablets for Cats and Dogs
	In cats
	
	- Marbofloxacin is indicated in the treatment of:
	  - skin and soft tissue infections (wounds, abscesses, phlegmons) caused by susceptible strains of organisms.
	  - upper respiratory tract infections caused susceptible strains of organisms.
	
	In dogs
	
	Marbofloxacin is indicated in the treatment of:
	- skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis,

	cellulitis) caused by susceptible strains of organisms. - urinary tract infections (UTI) caused by susceptible strains of organisms associated or not with prostatitis or epididymitis. - - respiratory tract infections caused by susceptible strains of organisms. - Efex 40 mg Chewable Tablets for Dogs In dogs Marbofloxacin is indicated in the treatment of: - skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis, cellulitis) caused by susceptible strains of organisms. - urinary tract infections (UTI) caused by susceptible strains of organisms associated or not with prostatitis or epididymitis. - respiratory tract infections caused by susceptible strains of organisms. Efex 100 mg Chewable Tablets for Dogs In dogs Marbofloxacin is indicated in the treatment of: - skin and soft tissue infections (skinfold pyoderma, impetigo, folliculitis, furunculosis, cellulitis) caused by susceptible strains of *organisms.* - urinary tract infections (UTI) caused by susceptible strains of organisms associated or not with prostatitis or epididymitis. - 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 hybrid applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	20th February 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Portugal, Romania, Spain,

I. SCIENTIFIC OVERVIEW

These applications were generic hybrid applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended. For generic hybrid applications, if there are differences in formulation from the reference product and/or bioequivalence with the reference product cannot be demonstrated through bioavailability studies, the applicant is required to submit pharmacological and toxicological data relevant to the user risk assessment (URA), including formulation specific data. Bioequivalence with a reference product was demonstrated, but the amount of active substance in the products differed to those of the reference products, therefore pharmacological and toxicological data were provided. The reference products were Marbocyl P 5 mg, 20 mg and 80 mg Tablets, authorised in the UK in June 2003.

The 10 mg tablets are indicated for use in both dogs and cats, while the 40 mg and 100 mg products are for use only in dogs. For the 10 mg product, for cats, the indication is for the treatment of skin and soft tissue infections caused by susceptible organisms. In dogs, the product is used to treat skin and soft tissue infections, urinary tract infections and respiratory tract infections caused by susceptible organisms. For the 40 mg and 100 mg products, the indication is to treat dogs with skin and soft tissue infections, urinary tract infections and respiratory tract infections caused by susceptible organisms. The recommended dose is 2 mg marbofloxacin/kg bw daily for up to 40 days, (indication dependent).

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.

II. QUALITY ASPECTS

A. Composition

The products contain marboflxacin and excipients lactose monohydrate, copovidone, silica (colloidal anhydrous), croscarmellose sodium, hydrogenated castor oil, pig liver powder, malted yeast and cellulose microcrystalline.

The container/closure systems are as follows:-

Efex 10 mg Chewable Tablets for Cats and Dogs

- (Polyvinyl chloride-Thermo-elast-Polyvinylidene chloride – aluminium heat sealed) containing 10 tablets per blister
- (Polyamide-Aluminium-Polyvinyl chloride – aluminium heat sealed) containing 10 tablets per blister

Cardboard box of 10 tablets containing 1 blister of 10 tablets
Cardboard box of 120 tablets containing 12 blisters of 10 tablets
Cardboard box of 240 tablets containing 24 blisters of 10 tablets

Efex 40 mg Chewable Tablets for Dogs

- (Polyvinyl chloride-Thermo-elast-Polyvinylidene chloride – aluminium heat sealed) containing 8 tablets per blister

Cardboard box of 8 tablets containing 1 blister of 8 tablets
Cardboard box of 16 tablets containing 2 blisters of 8 tablets
Cardboard box of 120 tablets containing 15 blisters of 8 tablets
Cardboard box of 240 tablets containing 30 blisters of 8 tablets

- (Polyamide-Aluminium-Polyvinyl chloride – aluminium heat sealed) containing 6 tablets per blister

Cardboard box of 6 tablets containing 1 blister of 6 tablets

[1] SPC – Summary of Product Characteristics.

Cardboard box of 12 tablets containing 2 blisters of 6 tablets
Cardboard box of 120 tablets containing 20 blisters of 6 tablets
Cardboard box of 240 tablets containing 40 blisters of 6 tablets

Efex 100 mg Chewable Tablets for Dogs

- (Polyvinyl chloride-Thermo-elast-P olyvinylidene chloride – aluminium heat sealed) containing 6 tablets per blister

- (Polyamide-Aluminium-Polyvinyl chloride – aluminium heat sealed) containing 6 tablets per blister

Cardboard box of 6 tablets containing 1 blister of 6 tablets
Cardboard box of 12 tablets containing 2 blisters of 6 tablets
Cardboard box of 120 tablets containing 20 blisters of 6 tablets
Cardboard box of 240 tablets containing 40 blisters of 6 tablets

Not all pack sizes may be marketed.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence 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. A fully validated direct compression process is used.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is marbofloxacin, an established active substance described in the European Pharmacopoeia (Ph. Eur). Data were submitted from three active substance master files (ASMF). The active substance is manufactured in accordance with the principles of good manufacturing practice, and the specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Excipients listed in a pharmacopeia are cellulose microcrystalline, lactose monohydrate, copovidone, croscarmellose sodium, castor oil (hydrogenated) and silica (colloidal anhydrous). Excipients not described in a pharmacopoeia are pork liver powder and malted yeast. Specifications provided for pork liver powder and malted yeast were considered acceptable.

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

Scientific data 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 have been satisfactorily demonstrated.

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 sites 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. Two production-scale batches and one pilot-scale batches were tested for stability of the finished product at 36 months at 25°C ± 2°C/60%/RH ± 5%, 6 months at 40°C ± 2°C/75%/RH ± 5% and 12 months at 30°C ± 2°C/65%/RH ± 5%. Satisfactory data were acquired, and the SPC states any storage requirements for the products.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- The products do not require any special temperature storage conditions.
- Tablet portions should be stored in the blister pack.
- Any tablet portions remaining after 72 hours should be discarded.
- Keep the blister in the outer carton.
- The shelf life of the product as packaged for sale is 3 years.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant provided suitable referenced data. Marbofloxacin is a member of the fluoroquinolone family, synthetic antibacterial substances with a broad spectrum of activity against many Gram-positive and Gram-negative bacteria and mycoplasmas. The antibacterial family act by inhibiting DNA gyrase, and blocking the replication and transcription of DNA.

Pharmacokinetics

The applicant provided suitable referenced data, in addition to an *in vitro* study provided to demonstrate bioequivalence to the reference products. The active substance is highly soluble and completely absorbed.

Toxicological Studies

The applicant has provided bibliographical data which show that the toxicity of marbofloxacin is well known. A CVMP[2] summary report for marbofloxacin and the Freedom of Information (FOI) Summary of Zeniquin (Pfizer Inc: FDA NADA no. 141-151) were submitted, and the applicant referred to these documents in support of these applications.

- Single Dose Toxicity

LD_{50}[3] values were described for mice and rats in the range of 1781 – 3772 mg/kg for oral dose, and 972 – 2094 mg/kg for subcutaneous injection. The active substance is of low oral toxicity with symptoms of acute toxicity including tremors, decrease in activity and convulsions. Marbofloxacin is a low level irritant of eyes and skin.

- Repeated Dose Toxicity

A thirteen-week repeat dose study in rats, where marbofloxacin was administered orally at doses of 0, 4, 50 and 600 mg/kg provided a NOEL[4] of 4 mg/kg bw/day. Increased mortality was noted at the highest dose, with an effect on male reproductive organs, with induced arthropathy at 50 and 600 mg/kg bw/day. In a thirteen-week study in dogs, where marbofloxacin was orally administered at 1, 4 and 40 mg/kg bw/day, a NOEL was also established of 4

[2] CVMP – Committee for Veterinary Medicinal Products.
[3] LD_{50} – 50% of lethal dose.
[4] NOEL – No Observable Effect Limit.

mg/kg bw/day. At 40 mg/kg bw/day, changes were noted in articular cartilage, and testicular tubular atrophy and spermatic granuloma were noted in two animals. A thirteen-week study in young animals with oral doses up to 6 mg/kg bw/day exhibited no adverse marbofloxacin-related effects.

- Reproductive Toxicity, including Teratogenicity

A two-generation study in rats administered 10, 70 or 500 mg/kg bw/day of marbofloxacin showed that animals receiving the highest dose exhibited toxic symptoms and impairment of male fertility. In females, pup weight and pup implant was reduced, and additionally there was increased pup mortality. Less severe but similar symptoms were noted at 70 mg/kg bw, and the NOEL was established as being 10 mg/kg bw/day.

- Mutagenicity

Marbofloxacin was found not to be mutagenic in *in vivo* studies in mouse bone marrow in micronucleus tests, and not mutagenic in *in vivo* UDS rat studies. A CVMP Summary Report (October 1999) described marbofloxacin as being mutagenic in some bacterial strains in the absence and/or presence of metabolic activity, and induced point mutations in cultured Chines hamster V79 cells in the absence of metabolic activity.

- Carcinogenicity (if necessary):

The CVMP Summary Report (October 1999) provided data which implied that marbofloxacin was not carcinogenic.

Other Studies

The fluoroquinolones are established as causing hypersensitivity reactions and marbofloxacin causes mild skin and eye irritation. The SPC therefore carries a suitable warning.

Observations in Humans

The active substance is not in use in human medicines. Therefore, no data were required for this section.

Microbiological Studies

The applicant provided bibliographical data, which were submitted in support of the pharmacodynamic section of the dossier. No further data were required.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that the product is for oral use only, and there will be minimal exposure to the outside environment. 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)

The applicant claimed a BCS[5]-based biowaiver in order to claim bioequivalence with a reference product. This was deemed acceptable.

IV.A Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data for pharmacodynamic and pharmacokinetic parameters, suitable for this type of application.
A BCS-based biowaiver application must satisfy the following requirements:-

i. The active substance has been proven to exhibit high solubility and complete absorption.

Three publications analysing the bioavailability of marbofloxacin in both target species were submitted. These established that the active substance was highly bioavailable in cats and dogs.

ii. Very rapid (more than 85% within 15 minutes) *in vitro* dissolution characteristics of the test and reference product have been demonstrated considering specific requirements.

The applicant submitted details of dissolution studies which confirmed that the dissolution times of reference and proposed products were comparable.

iii. Excipients that might affect bioavailability are qualitatively and quantitatively the same.

Excipients used in the preparation of the proposed product were well-known and

were not ascertained to interfere with the action of the active substance.

[5] BCS – Baseline Comparison System.

Tolerance in the Target Species of Animals

Bioequivalence was claimed between product and reference product, it was established that the target animal safety profile was the same for both product and reference product.

Resistance

The applicant provided data which was relevant to the reference product, in addition to new data. It was accepted that the resistance profile for the proposed products was the same as that of the reference product. Resistance to fluoroquinolones is most often seen in relation to mutation at the *gyrA* and *parC* genes. Resistance may be seen where one or both mutations occur in tandem with multidrug resistance efflux mechanisms. Suitable data on relevant MIC[6] for marbofloxacin were presented. The SPC was updated to reflect any new findings. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

Two palatability studies were provided. In the first study, a suitable number of cats were evaluated for acceptance of the test product versus a palatable reference product (Marbocyl P) and a non-palatable reference product (Marbocyl Vet). This was a blinded study with animals being randomly assigned to one of three groups/ Animals were given one or one and a half 10 mg and 20 mg tablets, respectively, daily for 3 days. Acceptance of the product s was scored, and any side effects noted. The primary end-point was a) a tablet taken from the floor or a saucer, or the hand, or b) refusal. The secondary end-point was the percentage of animals showing any adverse effects within 1 hour of consumption. Suitable statistical analyses were performed. It was found that the palatable products were more frequently taken, with palatability between the test product and the flavoured reference product being similar.

In dogs, a similar study was performed in order to ascertain voluntary acceptance of the proposed product. The 40 mg proposed product was compared to the 80 mg Marbocyl P Tablets for Dogs and 80 mg Marbocyl vet. The 80 mg Marbocyl Vet marbofloxacin tablet was used as a negative control, (based on acceptance tests). This was a blinded, three test, three period cross-over design, with 10 dogs randomly allocated to three groups. The dose regimen was either 1 tablet of the test product, 0.5 of a tablet of 80 mg Marbocyl P, or 0.5 of a tablet of 80 mg Marbocyl Vet. Behaviour with regard to taking the tablets and any adverse reactions following administration were monitored. Animals refusing the products were withdrawn from the study, and suitable statistical data were acquired. The test product was consumed more readily than

the unpalatable product, Marbocyl Vet, but not significantly more than the palatable reference product, Marbocyl P. In conclusion it was found that all the

[6] MIC – Minimum inhibitory concentration.

test products were satisfactory.

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.

(www.gov.uk/check-animal-medicine-licensed)