ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Actimarbo 100 mg/ml Solution for Injection for Cattle and Pigs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0460/001/DC
Name, strength and pharmaceutical form	Actimarbo 100 mg/ml Solution for Injection for Cattle and Pigs
Applicant	Ecuphar NV Legeweg 157-i 8020 Oostkamp Belgium
Active substance	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Cattle and Pigs
Indication for use	In cattle: • Treatment of respiratory infections caused by susceptible strains of *Pasteurella multocida*, *Mannheimia haemolytica* and *Histophilus somni*. • Treatment of acute mastitis caused by *Escherichia coli* strains susceptible to marbofloxacin during lactation. In pigs: • Treatment of Metritis Mastitis Agalactia syndrome 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 applications in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	24th April 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, The Netherlands, Portugal, Slovakia, Spain

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted under Article 13 (1) of Directive 2001/82/EC. The claim was based on 'essential similarity' with two reference products, Marbocyl 10% Solution for Injection and Marbocyl Solo 10% Solution for Cattle, marketed in the UK since 1997 and 2007 respectively. Slight variations between the composition of the excipients of the reference products and the proposed product were acceptable as being suitable for the claim made.

The product is intended for the following indications in cattle: treatment of respiratory infections caused by susceptible strains of *Pasteurella multocida*, *Mannheimia haemolytica* and *Histophilus somni,* and treatment of acute mastitis caused by *Escherichia coli* strains susceptible to marbofloxacin during lactation. In pigs, the product is intended to treat Metritis Mastitis Agalactia syndrome caused by susceptible strains of organisms.

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, the consumer 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 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. Bioequivalence with two reference products was established via the comparative analysis of marbofloxacin, gluconolactone, disodium edetate, metacresol, monothioglycerol and water for injections.

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. Sequential addition of the components is performed in a nitrogen atmosphere, followed by filtration, filling of vials and subsequent sterilisation according to methods described in the European Pharmacopoeia (Ph. Eur). Satisfactory process validation was carried out on two consecutive production batches of 200 litres filled into 20, 50 and 100 ml vials.

C. Control of Starting Materials

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. The active substance is monographed in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided. All excipients are monographed in the Ph. Eur.

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

Data were provided which confirmed that no materials of animal origin are use in the manufacture of the active substance or the excipients.

E. Control on intermediate products

Data were provided which described an in-process specification of the proposed product prior to filtration. These tests include those for appearance, weight per ml, pH, identification and bioburden.

F. Control Tests on the Finished 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. Tests include those for appearance, pH, extractable volume, particulate matter, identification of active substance, other ingredients and impurities, microbial preservation, sterility and the presence of bacterial endotoxins.

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 was supported. Stability data were also provided for the finished product. From these data, a shelf-life of 30 months as packaged for sale and 28 days once the immediate package is opened were established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf-life of the veterinary medicinal product as packaged for sale: 30 months.
- Shelf-life after first opening the immediate packaging: 28 days.
- Store in the original package in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant provided suitably 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. With greater affinity for bacterial DNA gyrase, marbofloxacin causes no adverse effects in the host species when used as recommended.

Pharmacokinetics

The applicant provided suitable bibliographical data which described the absorption, distribution and elimination of the active substance in the host species. Following intra-muscular administration, marbofloxacin is easily absorbed and has high oral bioavailability in many mammalian species. The volume of distribution was large in all studies presented for various species. In cattle the serum elimination half-life after intravenous injection is approximately 2 hours, and approximately 3 hours after intramuscular administration. In other species elimination is generally slower, ranging from 4.2 – 12.4 hours.

Toxicological Studies

The applicant provided bibliographical data which show that the toxicity of marbofloxacin is well known. Data from CVMP[2] summary reports for maximum residues limits were also provided.

- Single Dose Toxicity

LD_{50}[3] values were described for mice and rats in the range of 887.8 – 3772 mg/kg, with signs of toxicity including tremors and convulsions.

- Repeated Dose Toxicity

One study showed that when marbofloxacin was administered orally to mice at doses of up to 178 mg/kg bw for 30 days, no major adverse effects were observed. (No NOEL[4] observed).

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 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 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

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

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.

- Embryotoxicity, foetotoxicity (including teratogenicity)

Adult rabbits given oral doses of 10, 30 or 80 mg of marbofloxacin/kg/bw/day during the gestative period exhibited no evidence of teratogenicity, but at 80

mg/kg/bw the active substance was foetotoxic, with a NOEL of 30 mg/kg/bw. Maternal toxicity was noted at 30 and 80mg/kg but was not seen at 10 mg/kg.

In adult rats given oral doses of 10, 85 or 700 mg/kg bw/day during gestation, no evidence of teratogenicity was observed. At 700 mg/kg bw foetotoxicity was observed, with a NOEL demonstrated of 85 mg/kg bw. The NOEL for maternal toxicity 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. 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

No data were required for this section.

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:-

- People with known hypersensitivity to (fluoro)quinolones should avoid using this product.
- In case of contact with skin or eyes, rinse with plenty of water. Care should be taken to avoid accidental self-injection.
- Accidental self-injection can induce a slight irritation.
- In case of accidental self-injection, seek medical advice and show the label to the doctor.
- 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 was required. The assessment concluded that there will be minimal exposure to the outside environment. All PEC_{soil}[5] calculations submitted were below the trigger value of 100 µg/kg. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

As bioequivalence was demonstrated between the proposed product and the reference products, no residues data were required. The withdrawal periods for the proposed products are the same as those of the reference products:-

Cattle:

- Respiratory infections (intramuscular use, 8 mg/kg single dose)
  Meat and offal: 3 days
  Milk: 72 hours

- Acute mastitis (intramuscular or subcutaneous use, 2 mg/kg single daily injection for 3 to 5 days)
  Meat and offal: 6 days
  Milk: 36 hours

[5] PEC_{soil} – Predicted Environmental Concentration.

Pigs (sows):

- Intramuscular use
  Meat and offal: 4 days

MRLs

Maximum Residues Limits for the active substance (as shown in Table 1 of the annex to Commission Regulation (EU) No 37/2010.

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Marbofloxacin	Marbofloxacin	Bovine	50 150 150 150 75	Fat Kidney Liver Muscle Milk	None
		Porcine	150 150 150 50	Kidney Liver Muscle Skin & Fat	None

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Data were provided which illustrated the pharmacodynamics and pharmacokinetics of the proposed product. These are presented in Section IIIA of this document. No further details were required for clinical assessment.

Tolerance in the Target Species of Animals

Bioequivalence was successfully claimed between product and reference products. Therefore, no data were required in this section.

Resistance

Bibliographical references were submitted for this section of the dossier. The activity of marbofloxacin via the inhibition of DNA gyrase in bacterial species is concentration dependent in Gram negative bacteria and time dependent in Gram positive bacteria. Recognised bacterial resistance mechanisms to fluoroquinolones are chromosomal mutations that appear to be sited within a specific topoisomerase subdomain or via plasmid-mediated resistance. Data were presented which described the Minimum Inhibitory Concentration of marbofloxacin required to have effect on a variety of micro-organisms. These

results indicated that there was no significant increase in resistance from target bacterial species. The SPC carries suitable notification with regard to the occurrence of resistance.

IV.B Clinical Studies

Bioequivalence was successfully claimed between product and reference products. Therefore, no data were required in 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 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)