Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Quiflor 20 mg/ml Solution for Injection for Cattle, Pigs and Dogs
(AT, BE, DE, DK, ES, EL, IT, NL, PT, UK)
Quiflox 20 mg/ml Solution for Injection for Cattle, Pigs and Dogs
(CZ, HU, LT, LV, SK)

Quiflor 100 mg/ml Solution for Injection for Cattle and Pigs (Sows)

Quiflor S 100 mg/ml Solution for Injection for Cattle
(AT, BE, CZ, DE, DK, EL, HU, IT, LV, LT, NL, PT, SK, UK)
Quiflor Single Dose 100 mg/ml Solution for Injection for Cattle
(ES)

Date: 05 June 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0301/001/DC DE/V/0302/001/DC DE/V/0303/001/DC
Name, strength and pharmaceutical form	Quiflor 20 mg/ml Solution for Injection for Cattle, Pigs and Dogs Quiflor 100 mg/ml Solution for Injection for Cattle and Pigs (Sows) Quiflor S 100 mg/ml Solution for Injection for Cattle
Applicant	TAD Pharma GmbH Heinz-Lohmann-Str. 5 27472 Cuxhaven GERMANY
Active substance(s)	Marbofloxacin
ATC Vetcode	QJ01MA93
Target species	Quiflor 20 mg/ml Solution for Injection for Cattle, Pigs and Dogs: Cattle (pre-ruminant calves up to 100 kg b.w.), Pigs and Dogs Quiflor 100 mg/ml Solution for Injection for Cattle and Pigs (Sows): Cattle and Pigs (sows) Quiflor S 100 mg/ml Solution for Injection for Cattle: Cattle
Indication for use	Quiflor 20 mg/ml Solution for Injection for Cattle, Pigs and Dogs: Cattle (pre-ruminant calves up to 100 kg b.w): Treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida*, *Mannheimia haemolytica* and *Mycoplasma bovis*. Fattening pigs: Treatment of respiratory infections caused by sensitive strains of *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida*.

	Dogs: Treatment of infected wounds (including drained subcutaneous abscesses) due to Escherichia coli, Pasteurella sp. and Pseudomonas sp. Treatment of lower or urinary tract infections due to Escherichia coli and Proteus sp. The veterinary medicinal product should only be used based on susceptibility testing. <u>Quiflor 100 mg/ml Solution for Injection for Cattle and Pigs (Sows)</u>: Cattle: Treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma bovis*. Treatment of acute mastitis caused by Escherichia coli strains sensitive to marbofloxacin during the lactation period. Sows: Treatment of Metritis Mastitis Agalactia Syndrome caused by bacterial strains sensitive to marbofloxacin. The product should only be used based on susceptibility testing. <u>Quiflor S 100 mg/ml Solution for Injection for Cattle</u>: Treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*. This product should only be used based on susceptibility testing.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23 March 2011
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	AT, BE, CZ, DK, ES, GR, HU, LT, LV, NL, PT, SK, UK (former RMS)

I. SCIENTIFIC OVERVIEW

These applications for generic products were submitted in accordance with Article 13 (1) of Directive 2001/82/EC. The reference products are Marbocyl 2% solution for injection, Marbocyl 10% solution forinjection and Marbocyl Solo 10% solution for injection authorised in the UK by Vetquinol SA since June 1998, February 1997 and March 2007 respectively.

Quiflor 20 mg/ml solution for injection for cattle, pigs and dogs is authorised for use in cattle (pre-ruminant calves up to 100 kg b.w) and pigs. The product is authorised for treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida, Mannheimia haemolytica and Mycoplasma bovis*. In fattening pigs, the product can be used for the treatment of respiratory infections caused by sensitive strains of *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida*. In dogs the product is indicated for the treatment of infected wounds or subcutaneous abscesses and for urinary tract infections. The veterinary medicinal product should only be used based on susceptibility testing.

Quiflor 100 mg/ml solution for injection for cattle and pigs (sows) is authorised for use in cattle and pigs (sows). The product is authorised for treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma bovis* in cattle. The product can also be used for treatment of acute mastitis caused by *Escherichia coli* strains sensitive to marbofloxacin during the lactation period. In sows, the product can be used for the treatment of Metritis Mastitis Agalactia Syndrome caused by bacterial strains sensitive to marbofloxacin. The product should only be used based on susceptibility testing.

Quiflor S 100 mg/ml solution for injection for cattle is authorised for use in cattle for the treatment of respiratory infections caused by sensitive strains of *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*. The product should only be used based on susceptibility testing.

The products are produced and controlled using validated methods and tests, which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species; the slight reactions observed are indicated in the SPC[1]. The products are safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of each product was demonstrated according to the claims made in the SPC.

[1] SPC - Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

Quiflor 20 mg/ml solution for injection for cattle, pigs and dogs
Each ml of solution for injection contains 20 mg of marbofloxacin as an active substance and excipients gluconolactone, disodium edetate, mannitol, metacresol, monothioglycerol and water for injections.

The product is supplied in 50 ml, 100 ml or 250 ml amber glass Ph. Eur[2]. Type II bottles with bromobutyl rubber stopper and aluminium closure.

Quiflor 100 mg/ml solution for injection for cattle and pigs (sows)
Each ml of solution for injection contains 100 mg of marbofloxacin as an active substance and excipients gluconolactone, disodium edetate, metacresol, monothioglycerol and water for injections.

The product is supplied in 50 ml, 100 ml or 250 ml amber glass Ph. Eur. Type II bottles with bromobutyl rubber stopper and aluminium closure.

Quiflor S 100 mg/ml solution for injection for cattle
Each ml of solution for injection contains 100 mg of marbofloxacin as an active substance and excipients gluconolactone, disodium edetate, metacresol, monothioglycerol and water for injections.

The product is supplied in 100 ml or 250 ml amber glass Ph. Eur. Type II bottles with bromobutyl rubber stopper and aluminium closure.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

B. Method of Preparation of the Product

The products are 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.

C. Control of Starting Materials

[2] Ph. Eur - European Pharmacopoeia

The active substance marbofloxacin is the subject of a monograph in the European Pharmacopoeia. The supporting data have been provided in the form of EDMF[3]. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

There are six excipients used in the formulation of Quiflor 20 mg/ml solution for injection for cattle, pigs and dogs. Disodium edetate, mannitol, metacresol and water for injections have monographs in the European Pharmacopoeia and each complies with the requirements of the current edition of the Ph. Eur. Gluconolactone and monothioglycerol comply with the USP/NF[4]. This is considered acceptable.

The formulations of Quiflor 100 mg/ml solution for injection for cattle and pigs and Quiflor S 100 mg/ml solution for injection for cattle do not contain mannitol. These formulations contain gluconolactone, disodium edentate, metacresol, monothioglycerol and water for injections.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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. The satisfactory validation data for the analytical methods have been provided.

G. Stability

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. The shelf life of the veterinary medicinal product as packaged for sale is 3 years.

H. Genetically Modified Organisms

[3] European Drug Master File
[4] United States Pharmacopeia/The National Formulary

Not applicable

J. Other Information

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after opening the immediate packaging: 28 days

Special precautions for storage
Store in the original package in order to protect from light.
Do not freeze.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on pharmacology and toxicology were not required.

User Safety

The following 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.
- Avoid contact of the skin and eyes with the product. In case of accidental spillage onto skin or eyes, rinse the affected area with large amounts of water.
- Avoid accidental self-injection, since this can cause local irritation. In case of self-injection or 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 guidelines. The PEC_{soil}[5] values derived from several studies were

[5] Figure provided after calculation of the predicted concentration of active substance in the upper 5 cm of soil.

acceptable and in accordance with VICH[6] guidelines. 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

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on residues depletion were not required.

MRLs

MRLs[7] are listed below and the marker substance is marbofloxacin.

	Bovine	**Porcine**
Muscle	150 (µg/kg)	150 (µg/kg)
Liver	150 (µg/kg)	150 (µg/kg)
Kidney	150 (µg/kg)	150 (µg/kg)
Fat / skin	50 (µg/kg)	50 (µg/kg)
Milk	75 (µg/kg)	-

Withdrawal Periods

<u>Quiflor 20 mg/ml solution for injection for cattle, pigs and dogs</u>
Preruminating calves (up to 100 kg body weight)
Meat and offal: 6 days

Pigs:
Meat and offal: 4 days

Dogs:
Not applicable

<u>Quiflor 100 mg/ml solution for injection for cattle and pigs (sows)</u>
Cattle:
Meat and offal: 6 days

[6] International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.
[7] Maximum Residue Limit

Milk: 36 hours

Pigs:
Meat and offal: 4 days

Quiflor S 100 mg/ml solution for injection for cattle

Meat and offal: 3 days
Milk: 72 hours

IV CLINICAL ASSESSMENT (EFFICACY)

As these were generic applications according to Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, and the applicant claimed exemption from bioequivalence studies in accordance with paragraph 4.b) of the Guidelines for the conduct of bioequivalence studies for veterinary medicinal products, there was no requirement to submit any data to support this section. This is considered acceptable.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on target species tolerance studies were not required.

IV.B Clinical Studies

As these were generic applications according to Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, and the applicant claimed exemption from bioequivalence studies in accordance with paragraph 4.b) of the Guidelines for the conduct of bioequivalence studies for veterinary medicinal products, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product. No further data were submitted.

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 Veterinary Medicinal Agencies 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.

•	05 June 2018	Change in RMS from UK to DE.
•	26 October 2017	Change in contact details for local representative.
•	23 May 2017	Minor change in the manufacturing process of the finished product. (concerning DE/V/0301/001 only)
•	02 August 2016	Extension of retest period of active substance.
•	03 June 2016	Renewal – UK as RMS
•	24 November 2015	Mock-ups updated (concerning DE/V/0301/001 only)
•	20 May 2015	Change in manufacturing site of the active substance
•	22 April 2015	Addition of UK local representative information to package leaflet.
•	11 September 2014	Change to the product name in Czech Republic, Hungary, Lithuania, Latvia and Slovakia, from 'Quiflor' to 'Quiflox'. (concerning DE/V/0301/001 only)
•	12 May 2014	Addition of dogs as a target species. (concerning DE/V/0301/001 only)
•	28 March 2014	Addition of batch release site, change in shelf life of the finished product from 2 to 3 years and change in pack size of the finished product. (concerning DE/V/0301/001 only)
•	15 November 2013	Change to batch release arrangements. Change in shelf life of the finished product, from 2 years to 3 years. (concerning DE/V/0302/001, DE/V/0303/001)
•	28 August 2013	Change of MAH from Krka d.d. to TAD Pharma GmbH in DE.
•	08 March 2013	To change the QPPV for an existing pharmacovigilance system as described in the DDPS.
•	07 February 2013	Change in the manufacturing process of the active and deletion of an active substance manufacturer.

	23 January 2013	Change of MAH from Miklich Laboratorios S.L. to Krka d.d.