IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Marfloxin 20 mg/ml solution for injection for calves, pigs, dogs and cats

PRODUCT SUMMARY

EU Procedure number<?xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />	IE/V/0262/001/DC
Name, strength and pharmaceutical form	Marfloxin 20 mg/ml solution for injection.
Active substance(s)	Marbofloxacin
Applicant	Krka, d.d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia.
Legal basis of application	A generic application in accordance with Article 13.1 of Directive 2001/82/EC as amended. The reference product cited in the original application (for cattle and pigs) was Marbocyl 2% Solution for Injection (Vetoquinol Ireland Limited, VPA 10983/032/001). The reference product has been authorised within the Community for more than 10 years. The reference product cited for the additional target species (dog and cat) was Marbocyl SA 200 mg powder and solvent for solution for injection (Vetoquinol UK Limited) which is part of the Marbocyl global marketing authorisation. This is the same as the product Marbocyl 1% SA, powder and solvent for solution for injection, for cats and dogs authorised in Ireland (VPA 10983/037/001).
Date of completion of procedure	23rd March 2011
Target species	Calves (pre-ruminant and ruminant), pigs, cats, dogs
Indication for use	Treatment of infections due to marbofloxacin susceptible strains of bacteria. <u>In Calves</u> Treatment of respiratory infections caused by of *Histophilus somni*, *Mannheimia haemolytica* and *Pasteurella multocidad*. <u>In Pigs</u> Treatment of respiratory infections. Treatment of Metritis Mastitis Agalactia (MMA) syndrome. <u>In Dogs</u> Treatment of infected wounds and abscesses. Treatment of lower urinary tract infections due to *Escherichia coli* and *Proteus mirabilis.* Prevention of surgical infections due to *Staphylococcus intermedius*, *Escherichia coli* and *Pseudomonas aeruginosa*. <u>In Cats</u> Treatment of infected wounds and abscesses. Prevention of surgical infections due to *Staphylococcus intermedius*, *Escherichia coli* and *Pseudomonas aeruginosa*.
ATCvet code	QJ01MA93
Concerned Member States	BG, PL, RO, SI

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation

process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I SCIENTIFIC OVERVIEW

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.

The product is 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 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. Qualitative and Quantitative Particulars

The product contains 20 mg/ml marbofloxacin as the active substance and the following excipients: gluconolactone, disodium edetate, mannitol, metacresol, monothioglycerol and water for injections.

The product is packaged in 20 ml, 50 ml or 100 ml amber glass vials (Ph. Eur. type II) which are sealed with bromobutyl rubber stoppers and aluminium closures.

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 at 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

The active substance is marbofloxacin, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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.

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.

D. Control on Intermediate Products

Not applicable.

E. 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.

F. 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.

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 when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13.1 of Directive 2001/82/EC, as amended, and <?xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />

- For the target species cattle and pigs, acceptable justification for the omission of bioavailability studies to demonstrate bioequivalence with the reference product Marbocyl 2% Solution for Injection (Vetoquinol Ireland Ltd) has been provided, and
- For the target species dog and cat, bioequivalence with the reference product Marbocyl 1% SA, powder and solvent for solution for injection has been demonstrated following subcutaneous administration and a waiver from the need to conduct bioequivalence studies for the intravenous route of administration was accepted,

bioequivalence with the reference product can be accepted and the results of safety and residue tests or of pre-clinical and clinical trials are not required.
The safety and efficacy aspects of this product are identical to the reference products.

Warnings and precautions as listed on the product literature are in line with those of the reference products and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

Cattle and pig:

The test product has been formulated to include the same active substance and the same excipients in the same concentrations as the reference product Marbocyl 2% Solution for Injection. It can be accepted that the product is essentially similar to the reference product (Marbocyl 2%) in terms of the quantitative composition of both the active substance and excipients and that exemption from the requirement for *in vivo* bioequivalence data for calves and pigs is justified.

Dog and cat:

The applicant has conducted bioequivalence studies in both cats and dogs for the subcutaneous route of administration. It was concluded as follows:

- Cat subcutaneous study: The results of this study demonstrated that the 90% confidence interval for AUC lies within the narrower limits of 80.00 – 125.00%. The upper confidence interval for C_{max} falls outside the wider limit. It was accepted that the potential for higher C_{max} when the product is administered at the recommended dose has no implications for target animal safety or efficacy.

- Dog subcutaneous study: The results of this study indicated that the 90% confidence intervals for AUC and C_{max} lie within the narrower limits of 80.00 – 125.00%.

Based on the outcome of these studies, it was accepted that the test (Marfloxin 20 mg/ml solution for injection) and reference product (Marbocyl 1% SA powder and solvent for solution for injection) are bioequivalent when administered to cats and dogs by the subcutaneous route at a dose of 2 mg marbofloxacin/kg bw.

A waiver from the need to conduct bioequivalence studies for the intravenous route of administration was accepted.

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

No data provided given that bioequivalence with the reference products can be accepted.

Microbiological Studies

Given that bioequivalence with the reference products is accepted, Marfloxin 20 mg/ml is expected to demonstrate the same antimicrobial effect as the reference products against the target bacterial pathogens.

The excipients included in the test product are commonly used in injectable veterinary pharmaceuticals.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the same risk management measures for the reference products are applicable for Marfloxin 20 mg/ml solution for injection. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product and are in line with those agreed for other injectable fluoroquinolone containing products authorised through European procedures.

Environmental Risk Assessment

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 determined that all PEC_{soil} values fall below the trigger value of 100 µg/Kg. No additional warnings regarding the environment are therefore 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.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted because the formulation of the product is considered to be sufficiently similar to that of the reference product (Marbocyl 2% Solution for Injection) to be considered equivalent and thus bioequivalence with the reference product can be accepted.

MRLs

Marbofloxacin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	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	N/A

Withdrawal Periods

Based on the withdrawal periods of the reference product in the RMS, a withdrawal period of 4 days for meat & offal in calves and 2 days for meat & offal in pigs are justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Cattle and pig:

The test product has been formulated to include the same active substance and same excipients in the same concentrations as the reference product Marbocyl 2% Solution for Injection. It can be accepted that the product is essentially similar to the reference product (Marbocyl 2%) in terms of the quantitative composition of both the active substance and excipients and that exemption from the requirement for *in vivo* bioequivalence data for calves and pigs is justified.

Dog and cat:

The applicant has conducted bioequivalence studies in cats and dogs for the subcutaneous route of administration. It was concluded as follows:

- Cat subcutaneous study: The results of this study demonstrated that the 90% confidence interval for AUC lies

within the narrower limits of 80.00 – 125.00%. The upper confidence interval for C_{max} falls outside the wider limit. It was accepted that the potential for higher C_{max} when the product is administered at the recommended dose has no implications for target animal safety and efficacy.

- Dog subcutaneous study: The results of this study indicated that the 90% confidence intervals for AUC and C_{max} lie within the narrower limits of 80.00 – 125.00%.

Based on the outcome of these studies, it was accepted that the test (Marfloxin 20 mg/ml solution for injection) and reference product (Marbocyl 1% SA powder and solvent for solution for injection) are bioequivalent when administered to cats and dogs by the subcutaneous route at a dose of 2 mg marbofloxacin/kg bw.

A waiver from the need to conduct bioequivalence studies for the intravenous route of administration was accepted.

Tolerance in the Target Species of Animals

No studies in calves or pigs were conducted given that the product is essentially similar to the reference product. The same information in respect of expected adverse reactions as appears in the SPC of the reference product Marbocyl 2% Solution for Injection is included in the SPC of Marfloxin 20 mg/ml.
In the case of cats and dogs no tolerance studies were conducted, given that:

- Marfloxin 20 mg/ml and the reference products are the same in terms of pharmaceutical form,
- Bioequivalence with the chosen reference product is accepted,
- The proposed use of Marfloxin 20 mg/ml is the same as the authorised use for the reference product (same target species, same indication, same routes of administration, same dose and treatment regimen), and
- The information proposed for inclusion in the SPC of Marfloxin 20 mg/ml relating to target animal safety reflects the text approved for the reference product,

It was accepted that Marfloxin 20 mg/ml will not present any greater risk to the target animals than the minimal risk posed by the reference products.

Resistance

Adequate warnings and precautions appear on the product literature. The SPC includes MIC data for the target pathogens.

IV.B Clinical Studies

Field Trials

No field trials have been conducted given that the product is accepted as being essentially similar to the reference product.

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.

VI 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 HPRA website.

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.

Changes:

Quality Changes

Summary of change (Application number)	**Approval date**
Addition of a 20 ml pack size (IE/V/0262/1/II/003/G)	07/02/2014

Safety/Efficacy Changes

Summary of change (Application number)	**Approval date**
Addition of target species – cats and dogs (IE/V/0262/1/II/003/G)	07/02/2014