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

Fenflor 300 mg/ml Solution for Injection for Cattle

Date: 17 April 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0195/002/DC
Name, strength and pharmaceutical form	Fenflor 300 mg/ml Solution for Injection for Cattle
Applicant	KRKA d.d. NOVO mesto Smarjeska cesta 6 SLO-8501 NOVO MESTO Slovenia
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Cattle
Indication for use	Diseases caused by florfenicol susceptible bacteria. Preventive and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* The presence of the disease in the herd should be established before preventive treatment.

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	30 June 2010
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	Austria, Belgium, France, Ireland, Italy, The Netherlands, Poland, Portugal, Spain, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol contains 300 mg/ml florfenicol and is indicated for the treatment of cattle with florfenicol susceptible bacterial infections. In particular, preventive and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* The presence of the disease in the herd should be established before preventive treatment.

This is an application for an extension to the Marketing Authorisation for Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol to add a new route of administration (subcutaneous route), submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. Bioequivalence was claimed with the reference product, Nuflor Injectable Solution, which has been marketed in the UK since December 1994.

The product which consists of a light yellow to clear viscous liquid is delivered either intramuscularly or subcutaneously for treatment and subcutaneously for prevention.

For treatment, the dosage rate is 20 mg/kg bodyweight (1ml/15kg), twice, at an interval of forty eight hours intramuscularly and 40 mg/kg bodyweight (2ml/15kg) subcutaneously. For prevention, the dosage rate is 40 mg/kg bodyweight (2ml/15 kg) subcutaneously. The product should only be given in the neck of the animal and bodyweight should be assessed as accurately as possible in order to avoid under-dosing.

Fenflor 300 mg/ml Solution for Injection to Cattle florfenicol is not to be used in adult bulls intended for breeding purposes, and the product should not be used in cases of hypersensitivity to the active substance or any of the excipients.

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 used safely in the target species and 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

Quality data were originally supplied for Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol, and this data is included in this section. No further information for this extension application was required.

A. Composition

The product contains the active substance florfenicol and excipients dimethyl sulfoxide, propylene glycol and macrogol 400. The container system consists of 50 ml, 100 ml and 250 ml Type 1 amber glass vials, closed with bromobutyl rubber bungs, secured with an aluminium collar. The particulars of the containers and controls performed are provided and conform to the regulation. Data were provided on the viscosity, density and syringeability from a number of batches of the product. The batches were of varying ages, and samples were taken from batches kept at 5°C and 25°C. Long term stability of the product was validated from data relating to product stored for six years at 5°C, during which time no precipitation was seen.

The choice of formulation and the absence 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

Three excipients are heated and mixed to homogeneity prior to the addition of florfenicol. The solution is then filter-sterilised and poured into glass vials. The rubber closures for the vials are heat-sterilised, and validation data from three production-scale batches of the product were acceptable. All areas in which the product is prepared are appropriately sterile.

The product is 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

The active substance is florfenicol, an established active substance which does not have a monograph in the European Pharmacopoeia. The manufacturer provided details of a testing monograph, and this was considered acceptable. 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. Details of florfenicol were presented in an appropriate EDMF file. No heavy metals are used in the synthesis of the product, and potential impurities are tested for under HPLC analysis.

Batch analytical data demonstrating compliance with the specification have been provided. All excipients are monographed in the European Pharmacopoeia and additional information was provided on microbial purity. Glass vials are subject to tests on appearance, dimensions and capacity, surface hydrolytic resistance, light transmission and arsenic content. Bromobutyl rubber closures are tested for appearance, dimensions, capacity, penetration, fragmentation, sealing ability and chemical properties.

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

There are no intermediate products

F. Control Tests on the Finished Product

The final product is analysed with regard to appearance, content volume, density, degradation products, sterility and bacterial endotoxins. Satisfactory validation data were provided by the applicant with regard to a variety of parameters. An HPLC

assay was used to detect the content of the active ingredient. Florfenicol is stable in neutral conditions, moderately stable in acid and oxidising conditions, and highly unstable in alkaline conditions. The main degradation product in acid conditions is florfenicol amine, in neutral conditions, traces of thiamphenicol are seen, while in an oxidising and alkaline environment, a variety of degradation products are observed. Exposure to sunlight has a minor effect on the appearance of degradation products, but this is abrogated by the use of amber vials. Batch analysis data were provided on two sets of aseptically prepared product, and these data were acceptable.

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. Data from six pilot-scale batches from the product manufacturing site and the active substance manufacturing site were provided. Both manufacturing sites have appropriate Good Manufacturing Practice (GMP) status. Both the finished product and the active substance were subjected to accelerated stability studies in accordance with VICH guidelines, (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products). The accelerated studies were conducted at 25ºC/60% RH and 40ºC/75% RH in packaging representative of the commercial containers to be used. Storage data were supplied from both premises for three months and six months at 40ºC/75% RH, and for eighteen months and twenty-four months at 25ºC/60% RH. No adverse effects to the active substance or to the finished product were seen, a proposed retest interval of twenty-four months was therefore considered justified.

For the finished product, samples from three pilot test batches were subjected to long-term testing at 25ºC/60% RH under VICH conditions. Examinations were performed at three, six, nine, twelve, eighteen and thirty-six months. The same batches were subjected to accelerated testing at 40ºC and examined after three and six months storage. All samples were tested against the criteria for shelf-life specification and all degradation products were seen to increase moderately over thirty-six months. Under accelerated conditions, increase in degradation products hastened and was comparable to samples analysed at 25ºC/60% RH for thirty-six months. Temperature cycling of the batches (twenty-four hours at

-18ºC and twenty-four hours at 25ºC), produced no changes after three cycles.

Two commercial scale batches of the finished product at each pack size were also analysed. Samples were stored for twelve months at 25ºC/60% RH and at 30ºC/60% RH. Additionally, samples were observed over six months at 40ºC and under cycling conditions from 25-40ºC. All results were satisfactory.

A final test on potential interaction between the product and the closure showed that no unexpected degradation was caused to the product.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf-life of the product as packaged for sale is three years. Shelf-life after first opening of the container is twenty-eight days.

Special storage precautions:
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this application is an extension to the Marketing Authorisation for Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol to add a new route of administration, submitted in accordance with Article 13(1) of Directive 2001/82/EC, and bioequivalence with the reference product has been demonstrated, results of toxicological and pharmacological tests and clinical trials are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and consumers. An appropriate environmental risk assessment was submitted.

III.A Safety Testing

Other Studies

Studies on laboratory animals did not reveal evidence of embryotoxic or foetotoxic effects for florfenicol. However, there has been no assessment of the effect of florfenicol on bovine reproductive performance and gestation.

Microbiological Studies

Aseptic, filter sterilisation of the product was employed as opposed to heat sterilisation, which was not suitably effective.

User Safety

The following precautions are listed on the SPC and product literature:

- Care should be taken to avoid self-injection.
- In case of accidental self injection, seek medical advice and show the label to the doctor.
- Do not use the product in known cases of sensitivity to propylene glycol.

Ecotoxicity

The applicant provided a Phase II environmental risk assessment in compliance with the relevant guidelines.
The predicted no effect concentration (PNEC) values derived from several studies were acceptable and in accordance with VICH 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

Residue Studies

Bioequivalence with the reference product was demonstrated. However, differences at the injection site could occur and thus two residue depletion studies were conducted in cattle. In the first study, Fenflor 300 mg/ml Solution for Injection to Cattle, florfenicol was given intramuscularly at 20 mg/kg bodyweight, twice, forty-eight hours apart, to an appropriate number of cattle. Post-mortem examination took place at various time points for a variety of tissues, including material retrieved from the injection site. All tissue samples had residues below the Limit of Quantification (LOQ). In the second study, Fenflor 300 mg/ml Solution for Injection to Cattle florfenicol was given subcutaneously at 40 mg/kg body weight to an appropriate number of cattle. All tissue samples had residues below the Limit of Quantification (LOQ) and these results were acceptable.

MRLs

MRLs for florfenicol in cattle

	(µg/kg)
Muscle	200
Liver	3000
Kidney	300

Withdrawal Periods

The withdrawal periods for meat and offal by intramuscular and subcutaneous routes are thirty days and forty-four days respectively.

The product is not to be used in lactating animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this application is for a line extension to the Marketing Authorisation for Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol to add a new route of administration, submitted in accordance with Article 13(1) of Directive 2001/82/EC, the applicant has not submitted any new pharmacodynamic, systemic tolerance, resistance or clinical efficacy data. Consequent to the additional route of administration, there is an additional indication in line with the reference product Nuflor Injectable Solution 300 mg/ml:

Preventive and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* The presence of the disease in the herd should be established before preventive treatment.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Florfenicol is a broad spectrum, synthetic antibiotic which is effective against Gram-positive and Gram-negative bacteria. Florfenicol inhibits protein synthesis at the

ribosomal level and is generally considered bacteriostatic in action, although some bactericidal action has also been demonstrated. The drug is active against the majority of bacterial pathogens associated with bovine respiratory disease.

Pharmacokinetics

The studies provided demonstrated the bioequivalence of Fenflor 300 mg/ml Solution for Injection for Cattle florfenicol to the reference product, Nuflor Injectable Solution 300 mg/ml. A single intramuscular injection at a dose rate of 20 mg/kg bodyweight and a single subcutaneous injection at a dose rate of 40 mg/kg bodyweight was administered to an appropriate number of cattle in two separate studies. Blood samples were taken before administration of the products, and at a variety of time points subsequently. No injection site reactions were seen during the trial. AUC[1] (0-inf) was used to demonstrate bioequivalence in accordance with the bioequivalence guideline. Confidence intervals calculated from C_{max}[2] and AUC were within the stipulated range of 80-125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

No systemic tolerance data in the target species are presented as the application was submitted in accordance with Article 13.1 (a) (iii) of Directive 2001/82/EC. Tolerance data for intramuscular administration and subcutaneous administration of the product versus the reference product in cattle was submitted as part of the residue depletion study, and parameters examined included behaviour, changes in locomotion, pain, swelling, erythema, oedema, scar formation, scaling, temperature and injection site inspection. Diarrhoea was seen in a small proportion of animals treated with the product. The diarrhoea lasted for one to two days and was considered transient. No statistically relevant differences were found between treated groups, and no differences were noted on physical examination of the injection sites between animals treated with Fenflor 300 mg/ml Solution for Injection and the reference product. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Resistance data were not submitted as bioequivalence was demonstrated with the reference product.

[1] Area under the curve
[2] Maximum concentration

IV.B Clinical Studies

Clinical documentation was not submitted as this application is for an extension and bioequivalence was demonstrated with 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 risk benefit 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.

•	17 April 2018	Change in RMS from UK to DE.
•	13 April 2018	Changes to the quality control testing arrangements for the active substance – addition of a site where batch control / testing takes place. Changes to the quality control testing arrangements for the active substance – addition of a site where batch control / testing takes place.
•	26 October 2017	Change in contact details for local representative.
•	17 September 2015	Renewal – UK as RMS.
•	28 July 2015	Changes to labelling and packaging not connected with the SPC.
•	26 March 2015	Removal of a distributor.
•	15 March 2013	Change to increase the shelf life of the finished product from 2 years to 3 years.
•	03 February 2012	To add a new supplier for rubber stopper.
•	03 September 2010	New MA – Extension to add a new route of administration (subcutaneous route).
•	02 June 2010	To add a distributor.

•	29 September 2009	New MA (MRP).
•	14 August 2007	Change of Marketing Authorisation Holder.