ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Mycoflor 300 mg/ml Solution for Injection for Pigs Florfenicol

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0385/001/DC
Name, strength and pharmaceutical form	Mycoflor 300 mg/ml Solution for Injection for Pigs Florfenicol
Applicant	SP Veterinaria, S.A. Ctra. Reus Vinyols Km 4.1 Aptdo. 60 43330 Riudoms Spain
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Pigs
Indication for use	Treatment of acute outbreaks of respiratory disease caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol.

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	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	26 October 2011
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Belgium Bulgaria Cyprus Czech Republic Denmark France Germany Greece Hungary Ireland Italy Luxembourg The Netherlands Poland Portugal Romania Slovakia Spain

I. SCIENTIFIC OVERVIEW

Mycoflor 300 mg/ml solution for injection for pigs florfenicol contains the active substance florfenicol. The product is authorised for use in pigs, for the treatment of acute outbreaks of respiratory disease caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol. The product is administered intramuscularly and the recommended dosage is 15 mg/kg which is equivalent to 1 ml/20 kg bodyweight. The product should be administered into the neck muscle twice 48 hour apart.

This application was submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. Bioequivalence is claimed with the reference product and global Marketing Authorisation, Nuflor 300 mg/ml solution for injection for cattle, first authorised in the UK by Schering-Plough Ltd in December 1994. Nuflor swine 300 mg/ml solution for injection, which is the named reference product, of the same formulation, but for use in pigs was authorised in the UK in December 2002.

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 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. Composition

The product contains florfenicol as an active substance and excipients n-methylpyrrolidone and glycerol formal.

The container/closure system consists of colourless Type II glass vials closed with bromobutyl rubber closure and an aluminium cap or polypropylene vials closed with bromobutyl rubber closures and an aluminium caps. The vials are available in 100 ml or 250 ml size.

The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

[1] Summary of Product Characteristics

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.

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

C. Control of Starting Materials

The active substance florfenicol is an established active substance which is not described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice, and is analysed in accordance with an acceptable testing monograph.

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.

The excipient n-methylpyrrolidone is monographed in the Ph. Eur. The specification provided for Glycerol formal is in compliance with Pharmeuropa. This is considered acceptable.

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 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.

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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its 2 year shelf life.

In-use stability testing has been carried out on fresh and aged samples. This is adequate to justify a 28 day in-use shelf life.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Special precautions for storage:
Store the bottle in the outer carton in order to protect from direct sunlight.

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 28 days

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Since this generic application was submitted 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 applicant has provided a user safety assessment in compliance with the relevant guideline. The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Care should be taken to avoid accidental self-injection. In case of self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- Avoid direct contact with skin, mouth and eyes. If eye exposure occurs, flush eyes immediately with clean water. If skin exposure occurs, wash the affected area with clean water. If accidental ingestion occurs, rinse the mouth with plenty of water and seek medical advice immediately.
- Wash hands after use.
- People with known hypersensitivity to florfenicol should avoid contact with the product.

Ecotoxicity

The applicant provided a Phase I and Phase II Environmental Risk Assessment (ERA) in compliance with the relevant guidelines. The PEC_{soil}[2] values derived from several studies were acceptable and in accordance with VICH[3] 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.

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

[3] International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III.B Residues documentation

Residue Studies

The applicant conducted an injection site residue depletion study in pigs. Mycoflor 300 mg/ml solution for injection for pigs florfenicol was administered intramuscularly at 15 mg/kg bodyweight to an appropriate number of pigs. Post-mortem examination took place at various time points for a variety of tissues, including material derived from the injection site. The analytical method used to determine the residue levels was validated properly and the correct marker residue was analysed. All tissue samples had residues below the LOQ[4] at all time points.

MRLs

MRLs[5] are listed below and the marker substance is the sum of florfenicol and its metabolites measured as florfenicol-amine.

	Porcine
Muscle	300 (µg/kg)
Liver	2000 (µg/kg)
Kidney	500 (µg/kg)
Fat / skin	500 (µg/kg)

Withdrawal Periods

Pigs:
Meat and offal: 18 days

[4] Limit of Quantification
[5] Maximum Residue Limit

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacology

Pharmacodynamics:
Since this generic application was submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on pharmacodynamic were not required.

Pharmacokinetics:
An in vivo bioequivalence study was conducted to demonstrate bioequivalence between the reference product, Nuflor Swine injectable solution 300 mg/ml, and the generic, Mycoflor 300 mg/ml solution for injection for pigs florfenicol. A single subcutaneous injection at a dose rate of 15 mg florfenicol/kg bodyweight was administered to an appropriate number of pigs. Blood samples were taken before administration of the products, and at a variety of time points subsequently. AUC[6] was used to demonstrate bioequivalence in accordance with the bioequivalence guidelines. Confidence intervals calculated from Cmax[7] and AUC were within the stipulated range of 80 – 125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

The applicant conducted GLP compliant local tolerance study in pigs injected intramuscularly with the product. The animals were observed for changes in behaviour or locomotion, the local temperature was measured and the injection sites were examined for signs of swelling, redness and pain. The study concluded that were no alterations of general health and behaviour with the exception of diarrhoea. Diarrhoea due to administration lasted 1-2 days. The histological changes seen at the injection site were considered as a normal physiological response to the introduction of a foreign substance. No statistical differences were found between treated groups and / or the effects of the test or reference products for the physical examination of the injection site.

Resistance

Since this generic application was submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on this section were not required.

[6] Area under the curve
[7] Maximum concentration

IV.B Clinical Studies

Since this generic application was submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on clinical trials were not required.

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 Medicines Agencies (veterinary) (HMA(v)) 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.

None