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

Floron 40 mg/g Premix for Medicated Feeding Stuff for Swine

PuAR correct as of 06/07/2018 when RMS was transferred to CZ.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0344/001/DC
Name, strength and pharmaceutical form	Floron 40 mg/g Premix for Medicated Feeding Stuff for Swine.
Applicant	Krka Dd
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Pigs
Indication for use	The product is indicated for use in fattening pigs for the treatment and prevention of swine respiratory disease in infected herds, due to *Pasteurella mulocida* susceptible to florfenicol. The presence of the disease should be established in the herd before initiating preventative treatment.

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 application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28th April 2010.
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Czech Republic, France, Greece, Hungary, Italy, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 13 (1) for generic applications, under Directive 2001/82/EC, as amended. Bioequivalence was claimed with the reference product, Nuflor 40 mg/g Premix for Medicated Feeding Stuff for Swine. The product is intended for use in pigs, at a dose rate of 10 mg of florfenicol/kg bodyweight per day, equivalent to 250 mg Floron 40 mg/g Premix for Medicated Feeding stuff for Swine/kg bodyweight per day. The product is given for five consecutive days. The rate of incorporation of the premix into the feed may be increased in order to achieve the required dosage on a mg/kg bodyweight basis and to cater for actual feed intake. Adjustment may be made in accordance with the following:-

$$\frac{\text{250 mg of the veterinary medicinal product per kg body weight and day} \times \text{Average pig body weight (kg)}}{\text{Average daily feed intake (kg/animal)}} = \text{mg the veterinary medicinal product per kg of feed}$$

Florfenicol is a broad-spectrum phenicol antibiotic, effective against most Gram positive and Gram negative bacteria. Florfenicol inhibits protein synthesis at the ribosomal level and is bacteriostatic in action.

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. Composition

The product contains 40 mg/g florfenicol and excipients propylene glycol and calcium carbonate. Comparative dissolution studies showed that the generic product performed identically to the reference product.

The container system is a 1 kg sachet, formed with a PET/aluminium/polyethylene laminate, and is also available in 5 kg, 10 kg and 25 kg packets, consisting of a multi-wall paper sack lined with high density polyethylene. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence of stabiliser 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

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data for two batches of 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 is not described in the European Pharmacopoeia (Ph. Eur). The applicant proposed a testing monograph which was acceptable. The active substance is manufactured in accordance with the principles of good manufacturing practice, and is analysed in accordance with an acceptable testing monograph. Tests include those for appearance, identity, loss on drying, pH and related substances.

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.

One of the excipients, propylene glycol, is monographed in the Ph. Eur. Calcium carbonate, is not monographed, however, a raw material specification was provided.

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, 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. Tests include those for appearance, loss on drying, identity, and related substances. Batch analysis data on two 150 kg batches of product demonstrated compliance with the proposed specifications.

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. Pilot scale and production scale batches of florfenicol were subjected to long-term and accelerated stability tests in accordance with VICH[a] guidelines, at 25°C/60%RH and 40°C/75%RH, in commercially representative packaging. Data were supplied presenting results on batches stored for up to twenty-four months. A retest period of twenty-four months was considered justified.

Two batches of finished product were stored, contained in the various sizes of packaging. Stability tests were performed in accordance with VICH guidelines for up to twelve months at 25°C/60%RH, and six months at 40°C/75%RH. Resulting data, along with data on opened product and in-feed stability, confirmed the final designated shelf life.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: four years.

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

Shelf life of the product after first opening the immediate packaging: three months. Shelf life after incorporation into meal or pelleted feed: three months. The product does not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological studies, and studies of other effects were not required. The safety aspects of this product are identical to the reference product.

III.A Safety Testing

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. No additional information was required as this was a generic application, and bioequivalence was claimed with the reference product. As the product and the reference product are identical with regard to qualitative and quantitative composition, no new user risk assessment was required. User warnings are as follows:-

- Skin sensitisation may occur.
- Avoid skin contact.
- Do not handle this product in case of known sensitisation to propylene glycol.
- Handle this product with care to avoid exposure during incorporation of premix into feed and administration of medicated feeding stuff to animals, taking all recommended precautions.
- Wear either a disposable half-mask respirator conforming to European standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143, chemically resistant gloves, protective coveralls and goggles while incorporating the premix into feed.
- Wear gloves and do not smoke, eat, or drink when handling the product or medicated feeding stuff.
- Wash hands thoroughly with soap and water after use of the product or medicated feeding stuff.
- Rinse thoroughly with water in case of exposure.
- If you develop symptoms following exposure such as skin rash, you should seek medical advice and take the package leaflet or the label with you.

Ecotoxicity

The applicant provided first and second phase environmental risk assessments in compliance with the relevant guideline. The assessments concluded that the product did not pose an unacceptable risk for the environment.

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 bioequivalence was established with the reference product.

Withdrawal Periods

Based on the data provided above, a withdrawal period of fourteen days for meat and offal was justified.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

An in vivo bioequivalence study was submitted to evaluate the test product, Floron Premix, compared to the reference product, Nuflor premix.

Pharmacokinetics

A GLP-compliant, single-dose, two-way, cross-over study was performed to demonstrate the bioequivalence of Floron 40 mg/g Premix for Medicated Feeding Stuff for Swine with the reference product, Nuflor 40 mg/g Premix for Medicated Feeding Stuff for Swine. A suitable number of target animals were treated with 250 mg of either Floron 40 mg/g Premix for Medicated Feeding Stuff for Swine or the reference product. The products were given to the animals individually, via a medicated diet, to fasted pigs, at day 0 and day 7. Clinical observations were carried out daily, and blood samples taken at various time points. Statistical analyses were carried out on the products, and bioequivalence was established if the 90% confidence intervals for ratio of the means of [b] AUCi and [c] AUCt of florfenicol came within the 80%-125% thresholds, and if the 90% confidence intervals for the ratio of the means of C_{max} were within acceptable bounds. The calculated intervals fell within the stated narrow bioequivalence intervals. Therefore, it can be concluded from this study that Floron Premix and Nuflor Premix are bioequivalent in terms of the extent and rate of absorption of florfenicol.

[b] AUCi – Area under the curve above the baseline.
[c] AUCt – Total area under the concentration versus time profile to the last sampling time.

Tolerance in the Target Species of Animals

No tolerance data were required as the product demonstrated bioequivalence with the reference product.

IV.B Clinical Studies

As the product has demonstrated bioequivalence with the reference product, there was no requirement for data 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.

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