



FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT
FOR A VETERINARY MEDICINAL PRODUCT

AQUAFLOL 500 MG/G PREMIX FOR MEDICATED FEEDING STUFF
FOR RAINBOW TROUTS

Date: 13/02/2013

MODULE 1**PRODUCT SUMMARY**

EU Procedure number	FR/V/0250/001/MR
Name, strength and pharmaceutical form	Aquaflor 500 mg/g premix for medicated feeding stuff for rainbow trouts
Applicant	INTERVET INTERNATIONAL BV WIM DE KORVERSTRAAT 35 AN BOXMEER THE NETHERLANDS
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Rainbow trout (<i>Oncorhynchus mykiss</i>)
Indication for use	For the treatment and prevention of furunculosis in rainbow trout caused by <i>Aeromonas salmonicida</i> susceptible to florfenicol in freshwater fisheries. The presence of the disease should be established in the holding unit before initiating the treatment.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website <http://www.anmv.anses.fr/>

MODULE 3**PUBLIC ASSESSMENT REPORT**

Legal basis of original application	Full application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	24/10/2012
Date product first authorised in the Reference Member State (MRP only)	12/12/2011
Concerned Member States for original procedure	AT, BG, CY, CZ, DE, EE, EL, ES, FI, HU, IT, LT, LV, MT, PL, PT, RO, SI, SK

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 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 500 mg/g florfenicol as the active substance and the excipients lactose monohydrate and povidone.

The product is packaged in a foil-laminate bag consisting of polypropylene/ LDPE/ aluminium foil. The particulars of the containers and controls performed are provided and conform to the regulation.

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 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. 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.

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.

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 shelf life when stored under the approved conditions.

A shelf-life after incorporation into feed as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided data about the pharmacological activities (general pharmacology, mode of action) of florfenicol.

Florfenicol is a synthetic antibiotic which acts by inhibiting bacterial protein synthesis at the ribosomal level. In vitro studies have shown florfenicol to have a broad spectrum of activity which includes aerobic and anaerobic bacteria which are either Gram positive or Gram negative.

Combined with the MIC₉₀ data (see part IVa of this PUAR), it can be expected that the tested product will have a bacteriostatic effect and possibly a bactericidal effect towards *Aeromonas salmonicida*.

Pharmacokinetic studies have been conducted with florfenicol following a single oral administration of 10 mg/kg body weight to rainbow trouts at 10°C and 16°C. After oral administration of medicated feed containing the tested product, peak plasma concentrations of respectively 3.0 and 3.7 µg/mL were reached 13.7 and 10.9 hours after administration at 10°C and 16°C. Florfenicol oral bioavailability was 73.9% at 10°C and 66.3% at 16°C.

Pharmacokinetic parameters following a single intravenous administration of 10 mg/kg body weight at 10°C were: apparent volume of distribution at steady state: 0.909 L/kg, total body clearance: 0.075 L/h and the elimination half life: 8.8 hours. These values indicate the drug was well distributed.

Toxicological Studies

Florfenicol has been examined under MRL regulation. A comprehensive toxicity study program is available and a summary of the toxicological studies has been published in form of the MRL summary report.

Acute toxicity of florfenicol is low and the active is not genotoxic as shown in several in-vivo and in-vitro mutagenicity tests. Some effects on the male reproduction organs have been noted, namely testicular atrophy and increased numbers of spermatogonia in the epididymides.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a phase II risk assessment which concluded that the risk for terrestrial and aquatic compartment is acceptable.

It may be noted that the product should only be used in freshwater fisheries for the treatment of furunculosis in trout. A full benefit-risk analysis has not been performed for use in marine aquaculture, especially with regards to the environmental risk. .

III.B Residues documentation

Residue Studies

The applicant has conducted 3 residue depletion studies in rainbow trouts at the following water temperatures: 8°C, 10°C and 15°C. Samples of fish fillet (muscle + skin) were taken from animals at several time points. Results show that residues depleted to below the MRL before the end of the withdrawal period.

The analytical method was HPLC-UV based. The method was fully validated.

MRLs

Florfenicol is listed in Table I of Regulation (EU) No 37/2010 of 22 December 2009.

FLORFENICOL			
Species	Marker residue	Tissue	MRL
Fish	Sum of florfenicol and its metabolites measured as florfenicol amine	Muscle + skin in natural proportion	1000 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 135 Degree days is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species. In this study, a single administration of the final formulation at 1X, 3X and 5X the recommended dose showed a satisfactory margin of safety with regard to tolerance.

No side effect was observed after treatment of rainbow trouts with 5 times the recommended dose.

Resistance

The applicant has provided sufficient documentation to address the resistance of *Aeromonas salmonicida* to florfenicol in fish (including trouts).

Surveillance data of the susceptibility of target field isolates from fish collected between 1995 and 2009 across Europe show a MIC range of 0.12 – 32 µg/ml and a MIC90 of 1 µg/ml and a low percentage of non-wild-type isolates.

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted a controlled study with experimental infections at the recommended posology which shows that the tested product has a satisfactory efficacy towards furunculosis caused by *Aeromonas salmonicida*.

Field Trials

The applicant provided data from literature on the florfenicol treatment of furunculosis caused by *Aeromonas salmonicida* in rainbow trouts which support the efficacy of the tested product at the recommended dose.

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.

Note:

As the product is an antibiotic which could spread in the wild environment, the national competent authority had granted this marketing authorization under the following conditions:

- In order to assess the potential off-label use of this product in marine aquaculture, the applicant has been requested to supply the authorities with an annual follow up of sales and the geographic distribution of medicated feed prepared with this premix.
- Moreover, any document published by the applicant about this product will have to be approved by the authorities in first place.
- The applicant has also been requested to supply the authorities with an annual report about the *Aeromonas salmonicida* and *Aeromonas spp* sensitivity to florfenicol in fresh water fish production.