[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Aquaflor 500 mg/g premix for medicated feeding stuff for trouts
Finland: Aquaflor vet 500 mg/g premix for medicated feeding stuff for rainbow trouts
Aquaflor 500 mg premix for medicated feeding stuff

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:

Florfenicol 500 mg

Excipients:

Qualitative composition of excipients and other constituents
Lactose monohydrate
Povidone K29/32

A white free flowing powder.

3. CLINICAL INFORMATION

3.1 Target species

Trout - Golden/Rainbow/Redband/Steelhead (*Oncorhynchus mykiss*).

3.2 Indications for use for each target species

For the treatment and metaphylaxis of furunculosis in rainbow trout caused by *Aeromonas salmonicida* susceptible to florfenicol in freshwater fisheries. The presence of the disease should be established in the holding unit before initiating the treatment.

3.3 Contraindications

Do not use in broodstock.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not administer together with other antimicrobial products.

3.4 Special warnings

In order to maximize feed uptake throughout the population to be treated, medicated feed should be administered following the same feeding regimen as was used prior to treatment, to the greatest degree possible.
To minimize stress and ensure that all medicated feed is consumed in the infected shoal, daily feed may be reduced compared to the usual feeding rates.
Care should be taken when administering medicated feed by hand that feed pellets are widely dispersed to minimize hierarchical feeding behavior.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal 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.
Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to florfenicol.
The veterinary medicinal 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. The use of the veterinary medicinal product should always be combined with good management practices of the freshwater fisheries (e.g. vaccination programmes, biosecurity, water quality and site hygiene).

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

This veterinary medicinal product may cause hypersensitivity reactions (allergy) People with known hypersensitivity to florfenicol should avoid contact with the veterinary medicinal product.
Avoid inhalation of dust. Wear either a disposable half-mask respirator conforming to European standard EN 149 or a non-disposable half-mask respirator to European Standard EN 140 with a filter to EN 143
Avoid contact with the skin and eyes. Wear chemically resistant gloves, protective overalls and safety glasses while incorporating the premix into the feed.
Wear gloves and do not smoke, drink or eat while handling the product or medicated feed. Wash hands thoroughly with soap and water after use of the product or medicated feed. Clean thoroughly all equipment used for medicating feed.
In case of accidental self-ingestion seek medical advice immediately and show the package leaf-let or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

None known.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder <or its local representative> or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Not applicable.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

In-feed use. For the preparation of medicated feeding stuff.

The premix should be mixed into or on feed to deliver a total daily dose rate of 10 mg of florfenicol per kg body weight during 10 consecutive days.

The entire daily ration of medicated feed should be administered first for each day of the 10-day dosing period. If the feeding rate exceeds 0.4% of the biomass, non-medicated feed may be administered after the medicated ration, or a lower incorporation rate may be chosen for the preparation of medicated feed. If the feeding rate is ≤ 0.4% of the biomass, then the daily ration should consist of only medicated feed and be administered at one time.

Administration of medicated feed should begin immediately following diagnosis to ensure that fish are able to consume the complete medicated ration.

This veterinary medicinal product should be incorporated by licensed feed manufacturers only. An incorporation rate of 0.5% or 5 kg premix/ton feed is recommended; however, lower mixing rates can be used when higher feeding rates need to be covered. The concentration of medicated premix in feed should be ≥ 0.04% or 0.4 kg premix/ton feed.

Mixing Instructions:

During the preparation of medicated feed, the premix is either coated onto the surface of the pellet or incorporated into the feed ingredient mash prior to extrusion or pelleting.

Top-coating:

Method 1: The dry premix is thoroughly mixed with feed which typically contains 24 – 38% w/w lipid. Approximately 0.5 % w/w oil is then added to the premix/feed mixture to improve both premix adhesion and palatability.

a) Add known quantity of fish feed into a mixer.
b) Weigh the premix.
c) Mix premix with feed pellets.
d) Medicated feed pellets are mixed/coated with a predetermined amount of fish or vegetable oil.
e) At the completion of mixing, the veterinary medicinal product is transferred to a storage tank for packaging or transport.

Method 2: The dry premix is mixed with oil. The premix/oil preparation is then added to the feed to produce palatable medicated feed pellets.

a) Weigh out fish or vegetable oil into a bucket.
b) Weight out the premix and mix thoroughly with oil in the bucket
c) Add a known quantity of fish feed into a mixer.
d) Add the premix and oil mixture to the feed in the mixer, slowly, while the mixer is running at low speed. At the completion of mixing, the veterinary medicinal product is transferred to a storage tank for packaging or transport.

Extrusion or Pelleting:

The dry premix is added directly to the feed ingredient mash and mixed thoroughly. Water and steam are added, and the complete mixture is then extruded or pelleted, dried and packed.

a) The premix is added directly to the feed ingredient mash and mixed thoroughly to ensure homogeneity.
b) The mixture is steam pelleted and or extruded and the pellets are dried.
c) Medicated feed pellets are mixed/coated with a pre-determined amount of fish or vegetable oil.
d) At the completion of mixing, the veterinary medicinal product is transferred to a storage tank for packaging or transport

Recommended premix inclusion rate for preparation of medicated feed

Feeding Rate	Amount of premix per metric ton of feed	Amount of florfenicol per feed in mg/kg	Kilograms of fish medicated per metric ton of feed for 10-d treatment period
% biomass	kg	mg	kg
0.2	10	5000	50,000
0.3	6.7	3333	33,333
0.4	5	2500	25,000
0.5	4	2000	20,000
1.0	2	1000	10,000
2.0	1	500	5,000
3.0	0.66	330	3,300
5.0	0.40	200	2,000

The formula for calculation of the amount of premix to be added to feed to produce medicated feed at ≥ 0.4 kg premix/ton feed is as follows:

$$\frac{\text{20 mg premix (= 10 mg florfenicol) per kg body weight and day} \times \text{Average fish weight (kg)}}{\text{Average daily feed intake (kg/fish)}} = \text{mg premix per kg of feed}$$

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No adverse reactions were observed after treatment of rainbow trout with 5 times the recommended dose of florfenicol.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This veterinary medicinal product is intended to be used for the preparation of medicated feed.

3.12 Withdrawal periods

135 degree days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code : QJ01BA90

4.2 Pharmacodynamics

Florfenicol is a synthetic broad-spectrum antibiotic effective against most Gram-positive and Gram-negative bacteria isolated from domestic animals. Florfenicol acts by inhibiting protein synthesis at the ribosomal level. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in fish diseases notably *Aeromonas salmonicida.* Florfenicol is considered to be a bacteriostatic agent, but *in vitro* studies show that florfenicol demonstrate time-dependent bactericidal activity against *Aeromonas salmonicida*.
At present there are no accepted interpretive criteria for florfenicol MIC data of bacteria from aquaculture. However, a value of ≤ 4 µg/mL has been adopted by CLSI (2020) as the epidemiological

cut-off value for the determination of the wild-type population. *Aeromonas salmonicida* strains with a MIC ≤ 2 µg/mL are considered susceptible to florfenicol throughout Europe.

Surveillance data of the susceptibility of target field isolates from fish collected between 2012 and 2015 across Europe show a MIC range of 0.12 – 32 µg/ml and a MIC_{90} of 1 µg/ml and low percentage of non-wild-type isolates.
Florfenicol resistance in Gram-negative bacteria has been detected and is related to plasmid transfer of the flo gene. This gene codes for a membrane-associated exporter protein that promotes efflux of chloramphenicol and florfenicol. This can be located on plasmids carrying resistance to antimicrobials from other classes, therefore use of the veterinary medicinal product can select for co-resistance. Cross-resistance is limited due to the substitution of a hydroxyl group with a fluorine molecule. Therefore, florfenicol is less susceptible to resistance from bacteria expressing chloramphenicol acetyl transferase enzymes.

4.3 Pharmacokinetics

Pharmacokinetic studies have been conducted with florfenicol following a single oral administration of 10 mg/kg body weight to rainbow trout at 10° C and 16° C. After oral administration of medicated feed containing florfenicol, 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 had an oral bioavailability of 73.9% at 10° C and 66.3% at 16° C.

Pharmacokinetic parameters following a single intravenous administration of 10 mg/kg body weight were: apparent volume of distribution at steady state $V_{d(ss)}$ of 0.909 l/kg, total body clearance Cl_T of 0.075 l/h and the elimination half-life $T_{½\beta}$ of 8.8 hours. These values indicate the drug was well distributed.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packed for sale: 2 years
Shelf life after first opening the immediate packaging: 3 months
Shelf life after incorporation into meal or pelleted feed: 3 months

5.3 Special precautions for storage

Premix: The medicinal product does not require any special temperature storage conditions.
Store in a dry place.
Keep separate from feeds and foodstuffs.
Medicated feed: Do not store at temperatures above 25 °C.

5.4 Nature and composition of immediate packaging

2 kg laminated bag consisting of polypropylene/ low density polyethylene/ aluminium foil/ Surlyn ionomer heat sealant.

Pack sizes
Bag of 2 kg.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

{DD month YYYY}

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD month YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).