SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g premix contains:

Active substance:
Florfenicol 500 mg

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff.
A white free flowing powder.

4. CLINICAL PARTICULARS

4.1 Target species

Rainbow trout (*Oncorhynchus mykiss*)

4.2 Indications for use, specifying the 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.

4.3 Contraindications

Do not use in broodstock.
Do not use in animals with known hypersensitivity to the active ingredient.
Do not administer together with other antimicrobial products.

4.4 Special warnings for each target species

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.

4.5 Special precautions for use

Special precautions for use in animals
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.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to florfenicol.
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. The use of the 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
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 (locally available equivalent half-mask respirator), chemically resistant gloves, protective coveralls and safety glasses while incorporating the premix into the feed.

Wear gloves and do not smoke or eat while handling the product or medicated feed. Wash hands thoroughly with soap and water after use of the product or medicated feed. Thoroughly clean all equipment used in medicating feed.
In case of accidental self-ingestion seek medical advice immediately and show the label to the physician.
People with known hypersensitivity to the active ingredient should avoid contact with the veterinary medicinal product.

4.6 Adverse reactions (frequency and seriousness)

None.

4.7 Use during pregnancy, lactation or lay

Not applicable.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

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 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 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 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 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:

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

4.10 Overdose

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

4.11 Withdrawal periods

135 degree days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, Amphenicols, florfenicol
ATCvet code: QJ01BA90

5.1 Pharmacodynamic properties

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 (2006) 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 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.

5.2 Pharmacokinetic particulars

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone K29/32

6.2 Incompatibilities

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

6.3 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

6.4. Special precautions for storage

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

6.5 Nature and composition of immediate packaging

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

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

Any unused product or waste material derived from such veterinary medicinal product should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2011

10. DATE OF REVISION OF THE TEXT

October 2016

LABELLING AND PACKAGE LEAFLET

A. LABELLING

NOT APPLICABLE

B. PACKAGE LEAFLET

PACKAGE LEAFLET

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

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

Intervet International B.V.
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

Manufacturer for the batch release:

Intervet GesmbH
Siemensstrasse 107
A-1210 Vienna
Austria

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

1g premix contains 500 mg florfenicol.
A white free flowing powder.

4. INDICATION(S)

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.

5. CONTRAINDICATIONS

Do not use in broodstock.
Do not use in animals with known hypersensitivity to the active ingredient.
Do not administer together with other antimicrobial products.

6. ADVERSE REACTIONS

None. If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Rainbow trout (*Oncorhynchus mykiss*)

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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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.

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9. ADVICE ON CORRECT ADMINISTRATION

Mixing Instructions:

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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.
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d) Medicated feed pellets are mixed/coated with a predetermined amount of fish or vegetable oil.
e) At the completion of mixing, the 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.

e) Weigh out fish or vegetable oil into a bucket.
f) Weight out the premix and mix thoroughly with oil in the bucket
g) Add a known quantity of fish feed into a mixer.
h) 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 product is transferred to a storage tank for packaging or transport.

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10. WITHDRAWAL PERIOD

135 degree days

11. SPECIAL STORAGE PRECAUTIONS

Premix: The medicinal product does not require any special storage conditions.
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Medicated feed: Do not store at temperatures above 25 °C.

12. SPECIAL WARNING(S)

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.
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Wear gloves and do not smoke or eat while handling the product or medicated feed. Wash hands thoroughly with soap and water after use of the product or medicated feed. Thoroughly clean all equipment used in medicating feed.
In case of accidental self-ingestion seek medical advice immediately and show the label to the physician.
People with known hypersensitivity to the active ingredient should avoid contact with the veterinary medicinal product.

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

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

February 2019

15. OTHER INFORMATION

2 kg laminated sachet consisting of polypropylene/ low density polyethylene/ aluminium foil/ Surlyn ionomer heat sealant.
For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

16. EXPIRY DATE

EXP:
Once opened, use by

17. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

For animal treatment only - to be supplied only on veterinary prescription.

18. THE WORDS “KEEP OUT OF THE REACH AND SIGHT OF CHILDREN”

Keep out of the reach and sight of children.

19. MANUFACTURER´S BATCH NUMBER

Batch No.

20. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally.]