ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

AquaVac FNM Plus Emulsion for Injection for Fish Emulsion for Injection for Fish

PuAR correct as of 09/02/2018 when RMS was transferred to ES. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V0212/001
Name, strength and pharmaceutical form	AquaVac FNM Plus Emulsion for Injection for Fish Emulsion for Injection for Fish
Applicant	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ United Kingdom
Active substance	Inactivated *Aeromonas salmonicida* strains MT004 and MT423
ATC Vetcode	QI10AB01
Target species	Atlantic Salmon
Indication for use	For the reduction of mortality due to furunculosis disease caused by *Aeromonas salmonicida*

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	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	8th March 2007
Date product first authorised in the Reference Member State (MRP only)	27th July 2001
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

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 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains inactivated *Aeromonas salmonicida,* strains MT004 and MT423 ≥ 5 x 10^8 cells per ml per strain, and excipients formaldehyde and sodium chloride.

The container/closure system is a 500 ml crimp sealed high density polyethylene flat bottle. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strain, inactivating agent and absence of preservative are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

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 *Aeromonas salmonicida*, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with the European Pharmacopoeial (Ph. Eur.) monographs where these exist. For the substances where there is no such requirement the company has identified the source of the substance, explained how its quality is controlled and provided relevant certificates of analysis.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. Guidelines; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of

Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular appearance, viscosity, conductivity, specific gravity, sterility, inactivation test, free formaldehyde, fill volume, safety and potency.

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

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.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life: 2 years
In-use shelf life: 5 hours

Storage conditions:
Store under refrigeration (2ºC to 8ºC)
Protect from light.
Do not freeze.

III. SAFETY ASSESSMENT

Laboratory and field studies have been conducted on the safety and efficacy of the product in Atlantic salmon and details of batches used in these studies were provided.

Laboratory trials

The safety of the administration of one dose and an overdose in the target animal is demonstrated in laboratory studies. Safety was assessed clinically, over an appropriate time course, through observation and physical examination. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The adverse effects seen following administration of one dose and an overdose in healthy animals weighing less than the minimum recommended body weight, were minor, transient and resolved within an acceptable time frame.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used are listed in Annex II of Council Regulation 2377/90 and therefore can be included in products used in food producing animals without a maximum residue limit. A zero day withdrawal period has been set.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

No information is available on the interactions between this product and any other. It is therefore recommended that no other vaccine should be administered within 168 degree days (14 days at 12°C) before and after vaccination with this vaccine.

Field studies

The applicant has conducted 5 field studies into the safety of AquaVac FNM Plus Emulsion for Injection for Fish.

Three of the studies examined the long term safety of AquaVac FNM Plus Emulsion for Injection for Fish. The animals were vaccinated as recommended by the intraperitoneal route and transferred to the sea 6 months later. At between 8 and 14 months post vaccination a number of fish were examined for

the presence of vaccine reactions. Behaviour and health status were observed during this time. No mortality was reported and growth rates and conversions were reported to be similar pre and post vaccination.

A study was also carried out which demonstrated shorter term safety in Atlantic salmon vaccinated with a batch of AquaVac FNM Plus Emulsion for Injection for Fish. This study separated animals into vaccinates and controls whereby some fish were vaccinated with AquaVac FNM Plus Emulsion for Injection for Fish, some with alternative vaccines and some fish were given saline. Around 9.5 weeks later the fish were exposed to *Aeromonas salmonica.* Twenty-one days post exposure a sample of fish from each group were weighed and monitored. Fish were examined externally and internally for any adverse effects. Some slight adhesions were observed, no mortality was reported and growth rates and conversions were reported to be similar between the groups.

A further study was carried out whereby some Atlantic Salmon were vaccinated with the recommended dose of AquaVac FNM Plus Emulsion for Injection for Fish. Other fish were vaccinated with other furunculosis vaccines. Sixteen weeks post vaccination the fish were transferred to sea pens and observed; food quantity and water temperatures were recorded weekly and weighed monthly. A number of fish were sampled from each pen and monitored for the presence of *Aeromonas salmonicida*. The infection rate in the fish vaccinated with AquaVac FNM Plus Emulsion for Injection for Fish was much lower than in the other vaccine groups. No adverse reactions were observed and the study demonstrated that vaccination with AquaVac FNM Plus Emulsion for Injection for Fish does not result in noticeable long term lesions 18 months after vaccination.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the vaccine does not constitute an environmental hazard. No warnings in regards to environmental exposure from the use of AquaVac FNM Plus Emulsion for Injection for Fish are therefore required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that efficacy is supported by data from routine batch potency testing.

One study was carried out after safety testing whereby Atlantic salmon 19g–26g ±10% were vaccinated with either a single dose of AquaVac FNM Plus Emulsion for Injection for Fish or a saline control vaccine. The two groups of fish were placed in separate holding tanks for 26-28 days at 5-15°C water and were observed daily for mortality and adverse effects as part of the safety testing. After 26-28 days half of the vaccinates were placed in separate holding tanks 5-15°C water. Half of the control group were similarly transferred to an identical tank. Both of these groups were then exposed to an intraperitoneal injection of a virulent strain of *Aeromonas salmonicida*. The remaining two groups of fish were then transferred to separate holding tanks 5-15°C water. A number of fish (tagged for identification) that had been infected by the injection of virulent *Aeromonas salmonicida* were added to the tanks. Fish were monitored for 21 days until mortality ceased to occur. In both the injection challenge and co-habitation challenge most of the vaccinates survived. The opposite is true for the control group. The results indicated that vaccination of fish of standard antigen input resulted in reduced mortality when challenged 28 days after vaccination.

A different study was carried out whereby Atlantic salmon 15g–20g were vaccinated with either a single or double dose of AquaVac FNM Plus Emulsion for Injection for Fish, or a saline control vaccine. The groups of fish were placed in separate holding tanks for 28 days at 5-15°C water and were observed daily for mortality and adverse effects as part of the safety testing. After 28 days half of each group of vaccinates were placed in separate holding tanks 12°C water. Half of the control group were similarly transferred to an identical tank. These groups were then exposed to an intraperitoneal injection of a virulent strain of *Aeromonas salmonicida*. Fish were monitored for 21 days until mortality ceased to occur. Most of the vaccinates survived. The opposite is true for the control group. The study supports the claim that vaccination of minimum weight fish results in reduced mortality when exposed to a virulent strain of *Aeromonas salmonicida* at approximately 28 days after vaccination

Field Trials

The applicant has conducted field studies which provide information on the duration of immunity. The field trial data presented clearly show that AquaVac FNM Plus Emulsion for Injection for Fish vaccinated fish had lower mortality

during an outbreak of furunculosis 6 months after vaccination than did fish that were either unvaccinated or vaccinated with another vaccine, despite all those other fish being treated with antibiotics during the outbreak. The studies have been discussed in part III of this report.

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.

(www.gov.uk/check-animal-medicine-licensed)