ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

AquaVac ERM Oral, Oral Emulsion for Rainbow Trout

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

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0216/001/R/001
Name, strength and pharmaceutical form	AquaVac ERM Oral, Oral Emulsion for Rainbow Trout
Applicant	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ
Active substance(s)	*Yersinia ruckeri*
ATC Vetcode	QI10BB03
Target species	Rainbow Trout
Indication for use	Active immunization of rainbow trout, 26 g and above against Enteric Redmouth disease (ERM) to reduce mortality caused by the Hagerman Type I strain (serotype 01) of *Yersinia ruckeri*. The vaccine is indicated for use in fish that have been vaccinated by immersion with AquaVac ERM within the previous 4 to 6 months. The time to achieve full effect of the vaccination will depend on water temperature. In fish vaccinated by immersion 4.5 months previous to oral vaccination, vaccine efficacy was demonstrated under field conditions at water temperatures of 10°C, 21 days (210 degree days) after completion of the vaccine feeding protocol and protection was observed for the 3 month duration of the field trial.

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 32 (2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	01 March 2006
Date product first authorised in the Reference Member State (MRP only)	23 November 2001
Concerned Member States for original procedure	Austria, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Norway, Poland, Portugal, Slovakia, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

AquaVac ERM Oral, Oral Emulsion for Rainbow Trout is an inactivated bacterial vaccine which is intended for use in rainbow trout to reduce mortality due to enteric redmouth (ERM) disease. The vaccine is intended as a booster vaccination following priming vaccination with AquaVac ERM Concentrate for Dip Suspension for Rainbow Trout.

ERM is a sub-acute to acute systemic infection caused by the bacterium *Yersinia ruckeri*. It is principally a disease of rainbow trout but all salmonid species are considered as potential hosts and clinical disease has also been reported in other species. The disease is most severe in fingerlings at temperatures of 15°C - 18°C, whilst in larger fish the disease is less severe and more chronic. Whilst fish usually have to be exposed to large numbers of bacteria for the disease to develop, asymptomatic carrier infection can develop after exposure to low levels of bacteria and clinical disease may then occur as a result of increased stress. Whilst ERM has been controlled using broad spectrum antibiotics, resistance has developed in many areas. In addition, it has been reported that disease can recur after antibiotic treatment has finished. Thus, vaccines are considered the most economical and effective means of controlling the disease.

AquaVac ERM Oral, Oral Emulsion for Rainbow Trout consists of formaldehyde inactivated cultures of *Y. ruckeri* serotype I (Hagerman) in an oil emulsion. The inactivated virus is present at not less than 5 x 10^8 cfu/mL, RPS[1] > 60%. It is supplied in one litre containers. Vaccination is not recommended for fish

[1] RPS – Relative percentage survival (of rainbow trout).

intended as broodstock. The vaccine is administered orally to fish of not less than or 26 g weight in a 10-day feeding programme, in which feed pellets treated with the vaccine are administered.

II. QUALITY ASPECTS

A. Composition

The products contains Inactivated cells of *Yersinia ruckeri* (Hagerman type I strain), relative percentage survival in Rainbow trout >60% after vaccination.
The excipients are formaldehyde, sodium chloride solution, fish oil and lecithin.

The product is supplied in sterile one litre, high density polyethylene bottles, capped with red bromobutyl stoppers and sealed with aluminium overseals. The bottles and stoppers comply with the requirements of the European Pharmacopoeia. There is no pharmacopoeial monograph for the aluminium overseals as these do not come into contact with the product.

The choice of the vaccine strain and inactivating agent are justified. The inactivation process and the detection limit of the control of inactivation are correctly validated. 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

AquaVac ERM Oral, Oral Emulsion for Rainbow Trout has been developed for the active immunisation of susceptible rainbow trout against enteric redmouth disease and may be used as a booster vaccination following primary vaccination with AquaVac ERM Concentrate for Dip Suspension for Rainbow Trout. Its main effect is to reduce mortality. The Hagerman Type I strain of *Y. ruckeri* was chosen for inclusion in the vaccine because it is the most common and most virulent serotype, and vaccines based on Type I strains appear to be protective against infection by other serotypes.

The product has a simple formulation, in which the aqueous phase consists of a suspension of inactivated bacteria suspended in saline and an oil phase.

Vaccine Antigen

There is no pharmacopoeial monograph for the active substance, *Y. ruckeri*. It was first obtained from a diseased rainbow trout in the Hagerman Valley region of Idaho in 1976. It was stored on a suitable culture medium and, when needed, the stock was expanded by inoculating some of the bacteria into rainbow trout and collecting the new bacteria from the kidneys of these fish. The stock bacteria are now stored in a freeze-dried state, using a stabilising solution.

When required for manufacture of the product, a bulk supply of bacteria is produced using a well-established microbial culture process in which a sample of stock bacteria is taken and successively cultured under controlled conditions

until there are enough bacteria to start a culture in a production-scale fermentation vessel. This culture is monitored to determine the time of optimum bacterial growth. At this stage, the pH of the culture is adjusted and the bacteria are inactivated by the addition of formaldehyde, a process which had been shown to be effective.

Checks are made to ensure that the correct bacteria have been produced, that they are not contaminated with other organisms or agents and that they have been inactivated.

Other Substances

The other substances include the formaldehyde solution which is used to inactivate the bacteria, hydrochloric acid, sodium hydroxide, sodium chloride and purified water, all of which comply with the relevant requirements of the European Pharmacopoeia. The stabilising solution in which the bacteria are stored includes some substances which comply with the requirements of the European Pharmacopoeia and others for which there are no such requirements. In this latter case, the company has identified the source of each substance, explained how its quality is controlled and provided relevant certificates of analysis. Not listed in a pharmacopoeia are the working and master seeds, bovine serum albumin, tryptone broth, fish oil and lecithin.

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

Vaccine Antigen

There is no pharmacopoeial monograph for the active substance, *Y. ruckeri*. It was first obtained from a diseased rainbow trout in the Hagerman Valley region of Idaho in 1976. It was stored on a suitable culture medium and, when needed, the stock was expanded by inoculating some of the bacteria into rainbow trout and collecting the new bacteria from the kidneys of these fish. The stock bacteria are now stored in a freeze-dried state, using a stabilising solution.

When required for manufacture of the product, a bulk supply of bacteria is produced using a well-established microbial culture process in which a sample of stock bacteria is taken and successively cultured under controlled conditions until there are enough bacteria to start a culture in a production-scale fermentation vessel. This culture is monitored to determine the time of optimum bacterial growth. At this stage, the pH of the culture is adjusted and the bacteria are inactivated by the addition of formaldehyde, a process which had been shown to be effective.

Checks are made to ensure that the correct bacteria have been produced, that they are not contaminated with other organisms or agents and that they have been inactivated.

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

All components of the product have been demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

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 product is manufactured in accordance with Good Manufacturing Practice and, where applicable, conditions, equipment and materials are sterile. The volume of active ingredient is calculated and mixed with the required quantity of saline to give the desired concentration of bacteria in the finished product. The pH is adjusted if necessary.

In-process control tests have been described in detail, and include tests for sterility, inactivation of the bacteria, amount of residual formaldehyde, pH, appearance, extractable volume, viscosity and conductivity.

All components of the product have been demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

Finished Product Quality Control

The tests conducted after manufacture include checks on the appearance of the product and its sterility, the safety and potency of the product for rainbow trout, and the amount of product that can be removed from the containers.

The results of the tests on three batches of the product have been provided and these demonstrate that a product which consistently meets the agreed specification can be produced

G. Stability

Finished Product
The product has a shelf-life of 24 months.

In-Use
The entire contents must be used after first opening. Any opened, unused vaccine should be disposed of. The product should be stored in a refrigerator at between 2°C - 8°C, and should be protected from light. The product is not to be frozen. Vaccine treated feed should be stored at 20°C ± 5°C in a dry, dark place.

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

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The entire contents must be used after first opening. Any opened, unused vaccine should be disposed of. The product should be stored in a refrigerator at between 2°C - 8°C, and should be protected from light. The product is not to be frozen. Vaccine treated feed should be stored at 20°C ± 5°C in a dry, dark place.

III. SAFETY ASSESSMENT

Introduction

Aquavac ERM Oral, Oral Emulsion for Rainbow Trout is an inactivated vaccine intended for oral administration in feed, given according to the following schedule:-

Vaccine treated food for five days.
Normal food for five days.
Vaccine treated food for five days.

Fish receive 0.1 ml of vaccine over the period of the regime, the product being used as a booster vaccine in fish of at least 26 g which have been primed as fry by either immersion or oral vaccination with AquaVac ERM, a related, previously authorised product, now authorised as AquaVac ERM Concentrate for Dip Suspension for Rainbow Trout. Safety data were generated using one of two formulations, which were essentially the same apart from diluents. The use of different diluents was deemed to have no impact on the finished product. Some assays cited were performed in order to test both the safety and efficacy of the product, (numbered correspondingly).

Laboratory trials

The laboratory has had GLP[2] accreditation since 2002 and prior to this, when some studies were performed, worked to GLP principles.

The first study (1) observed the safety of a single dose in non-boosted fish. Three groups of 50 rainbow trout, weighing between 1.0 g and 1.25 g were treated with AquaVac ERM and Aquavac ERM Oral, (a previously authorised version of the same product, results considered acceptable for this application). AquaVac ERM was administered as an immersant at a one in ten dilution, for 30 seconds. AquaVac ERM Oral was administered after mixing with the diet and feeding for 2 5 day periods separated by a 5 day period in which a normal diet was offered. Either oral or immersion booster vaccinations were given 30 days

[2] Good Laboratory Practise.

later, and challenges performed for potency evaluation 30 days after the booster. Prior to challenge no deaths occurred which were attributable to the vaccination regime. This demonstrated that the product could safely be used in fish of 2 g, this being below the recommended booster weight. These data were also used for efficacy testing.

A further study (2) was described in which a group of 200 10 g fish were vaccinated by immersion in AquaVac ERM, diluted one in ten, for 30 seconds. 50 fish were not vaccinated and acted as negative controls. 28 days later, the two groups were divided into 4 groups of 50 fish, and were vaccinated with AquaVac ERM Oral vaccine. Two batches of AquaVac ERM were used. For each batch, one group of fish was administered vaccine via the diet as recommended, a second group were administered the vaccine at twice the recommended dose, in the diet as recommended. A further 200 fish were dosed with AquaVac ERM at the single dose and double dose, but were not given the primary vaccination. All fish were observed for 28 days and then challenged. No deaths occurred in any group receiving AquaVac ERM Oral, irrespective of the fish being given the primary dose or not. No adverse effects were seen after vaccination, demonstrating that the product were safe to use in fish below the recommended weight.

Overdose studies were performed using the vaccine as either a primary or booster vaccination. In one study a group of rainbow trout weighing 18 – 20 g were given ERM Oral vaccine at double the recommended dose, mixed with the diet. The second group were used as negative controls. The fish were observed for 28 days, with no deaths being attributable to the vaccine.

In a further study, a group of 20 g rainbow trout were vaccinated with Aquavac ERM by immersion. A second group of 50 fish were untreated as negative controls. 28 days later vaccinated fish were given AquaVac ERM Oral vaccine at a double dose. The control group received a normal diet. All fish were studied for 28 days. An additional study observed the same protocol but in a 6 g group of fish. No adverse reactions were seen in any of the studies, demonstrating that a soluble dose of AquaVac ERM Oral was safe as a booster vaccine at twice the recommended dose, in fish smaller than the recommended size.

No formal laboratory studies were performed to determine the safety of the repetition of a single dose because it was considered that the dosage regimen is effectively a repeat dose administration, in that the product is administered over a period of days. The safety of the administration of a single dose has been demonstrated in a field trial in fish below the minimum weight. This is acceptable.

The product is not intended for use in broodstock, therefore there are no data with relevance to reproductive performance. The SPC carries appropriate warnings.

Field studies

A suitable number of fish fry (mean weight 3.5 g on arrival at facility), were vaccinated with Aquavac ERM and boosted with AquaVac ERM Oral four months later (3). No adverse effects were seen.

In a second study, the safety and efficacy of AquaVac ERM and AquaVac ERM Oral as booster were analysed (4). A suitable number of fish (mean weight 3.94 g), were vaccinated with AquaVac ERM using the recommended protocol. The fish were then divided into four groups. After 4 months, booster vaccinations were given. One group was boosted via intraperitoneal injection with 0.1 ml of AquaVac ERM, the second group were given AquaVac ERM Oral. No adverse reactions were seen that were attributable to the vaccine.

A third study investigated the safety and efficacy of AquaVac ERM vaccine administered both orally and via injection, followed by a booster vaccination with AquaVac ERM Oral (5). A suitable number of fish were primed by immersion in AquaVac ERM, and six months later, a proportion of the fish were given a booster dose of AquaVac ERM Oral. Other groups of fish were boosted with AquaVac ERM by injection, or not boosted. No adverse reactions were seen due to the boosting regimes.

A fourth study investigated the use of AquaVac on a farm with a history of ERM and vibriosis (6). A suitable number of fish were formed into a treatment group and control group. The treated group were vaccinated via immersion for 60 seconds in a mixture of AquaVac ERM and AquaVac Vibrio. 77 days later, the primed group were boosted with AquaVac ERM Oral and AquaVac Vibrio Oral. No adverse reactions were observed.

Four further fish-growing farms with a history of ERM disease were used in field trials (7). Primary vaccinations were given with AquaVac ERM Oral followed by booster vaccination 44 and 64 days afterwards. No adverse reactions were noted.

CONCLUSIONS ON SAFETY AND RESIDUES

The company provided data which comply with the legal requirements and provide adequate information to assess the safety of the product.

The laboratory tests and field trials demonstrated the overall safety of the vaccine for rainbow trout weighing 26 g and over, when administered as recommended. Overdose studies showed that the product has a good margin of safety. There has been no evaluation of the effects of the vaccination on reproductive performance as the vaccine is not intended for use in broodstock. A zero days withdrawal period is acceptable.

Conclusions on User Safety

It is recommended that rubber gloves should be worn during the vaccination procedure and protection should be taken against particle droplets inhalation, i.e. a dust mask should be worn when spraying and mixing vaccine onto feed pellets.

Conclusions on Consumer Safety

None of the ingredients of AquaVac ERM Oral are such as would cause unacceptable residues in treated fish. There is no need for a withdrawal period and there are no consumer safety concerns.

Ecotoxicity

An environmental risk assessment indicates that the risk to the environment from the use of AquaVac ERM Oral in rainbow trout is minimal. The product is formaldehyde inactivated and contains no live organisms. Fish are vaccinated in an enclosed environment with waste water being commonly channeled through settling tanks before release into a waterway, with spent vaccine being diluted in farm drainage. In addition, the fish oil in the product makes the pellets hydrophobic, which minimizes leaching into the environment. General advice for the disposal of any unused product is provided in the summary of product characteristics:

Any unused vaccine should be disposed of in accordance with national requirements.

The approved product label in different member states may provide further information on how to meet these requirements.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

The vaccine is intended for use as a booster vaccine of rainbow trout weighing 26 g and above that have been previously primed by immersion with AquaVac ERM Concentrate for Dip Suspension for Rainbow Trout.

Laboratory and field efficacy studies have been conducted on the product, and details of the batches used in these studies were provided. In addition to successful challenge potency testing, the applicant provided data from several tests to investigate the efficacy and safety of the product in fish. Some of the studies were also used to provide safety data and have been numbered correspondingly.

Laboratory Trials

The first study was also used to provide data for safety testing (1). Protection at RPS[3] 66% was provided after oral priming with AquaVac ERM, followed by boosting with AquaVac ERM Oral which provided an RPS of 88%.

In a second study (2), prime and booster vaccination (AquaVac ERM followed by AquaVac ERM Oral), offered a 95% and 98% level of protection respectively when used at the recommended dose. Oral administration alone provided 82% and 86% protection respectively.

[3] RPS – Relative Percentage Survival.

Field Trials

In the first study, a suitable number of rainbow trout fry were vaccinated via immersion with AquaVac ERM, the fish were then split into three groups (3). A second batch were vaccinated with AquaVac ERM then boosted with AquaVac ERM Oral four months later, with observations following for another three months. Results of mortality test indicated that the booster vaccination of AquaVac ERM Oral should take place 4 to 6 months after primary vaccination.

A second study observed the safety and efficacy of AquaVac ERM and AquaVac ERM Oral given as booster vaccinations in farmed rainbow trout (4). Efficacy was assessed by the measurement of the fish resisting natural challenge. Results were acceptable, despite this being a curtailed study.

A third study confirmed the efficacy of AquaVac ERM Oral when used under field conditions, when the fish were at high risk from ERM due to raised water temperature and the presence of ERM on the farm (5).

A fourth study (6) calculated an RPS of 87.63% for vaccinated groups.

Further studies on four fish-growing farms with a history of ERM disease. The contribution of these studies to the efficacy portion of the application was minimal (7).

CONCLUSIONS ON EFFICACY ASPECTS

The laboratory studies showed that the recommended regimen of immersion vaccination followed by boosting with AquaVac ERM Oral was effective at reducing or even preventing mortality due to ERM disease. At a water temperature of 12°C, immunity was shown to have fully developed by 28 days after vaccination and to last for 78 days.

It is noted that the development of immunity in fish is affected by the water temperature. The data in these studies were collected from fish kept in water at a constant 12°C, and the advice to users of the product therefore explains that the time in field conditions will depend on the temperature. At 12°C it takes 28 days, which is expressed as 12 x 28, i.e. 336 degree days. If the temperature is lower, the actual number of days will increase and if it is higher the actual number of days will decrease.

Field trials on commercial fish farms confirmed the efficacy of the product and indicated that mortality was reduced over longer periods in fish receiving a booster vaccination of AquaVac ERM Oral.

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)