ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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**(Reference Member State)**

**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

# AquaVac RELERA Concentrate for dip suspension or suspension for injection for Rainbow Trout

# MODULE 1

## PRODUCT SUMMARY

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| EU Procedure number | UK/V/0301/001/DC |
| Name, strength and pharmaceutical form | Aquavac Relera. 5 x $10^9$ cfu/ml (pre-inactivation) fixed target antigen input. RPS* for both bacterial species $\geq$75%. Concentrate for dip suspension or suspension for injection. Suspension in brown aqueous liquid. |
| Applicant | Schering-Plough Animal Health<br>Breakspear Road South<br>Harefield<br>Middlesex UB9 6LS |
| Active substance(s) | Inactivated cells of *Yersinia ruckeri* (Hagerman type 1 strain). Inactivated cells of *Yersinia ruckeri* (EX5 biotype strain). |
| ATC Vetcode | QI10BB03 |
| Target species | Rainbow trout |
| Indication for use | Active immunisation against Enteric Redmouth disease (ERM) to reduce mortality caused by Hagerman type 1 and EX5 biotype strains of *Yersinia ruckeri*. |

* relative percentage of survival in rainbow trout.

# 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

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|---|---|
| Legal basis of original application | Decentralised application in accordance with Article 12 of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 15th June 2009 |
| Date product first authorised in the Reference Member State (MRP only) | Not applicable |
| Concerned Member States for original procedure | Austria, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Norway, Poland, Slovakia, Slovenia, Spain. |

# I. SCIENTIFIC OVERVIEW

The bacterium *Yersinia Ruckeri* causes Enteric Redmouth disease seen principally in rainbow trout. Hagerman Type 1 is the most common and virulent strain of *Yersinia Ruckeri*, and vaccines based on Type 1 strains appear to be protective against other serotypes. However a new biotype, EX5, has caused problems for fish producers as the Hagerman strain is not cross-protective. Schering-Plough currently hold a Marketing Authorisation for a monovalent vaccine containing Hagerman Type 1 antigens, (Aquavac ERM). Aquavac Relera contains both Hagerman Type 1 and EX5 antigens in order to combat both strains of *Yersinia Ruckeri*.

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 reflected 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 cells of *Yersinia ruckeri* (Hagerman type 1 strain), and inactivated cells of *Yersinia ruckeri* (EX5 biotype strain) at 5 x $10^9$ cfu/ml (pre-inactivation), with residual formaldehyde and saline as excipients.
The container is a high-density polyethylene bottle closed with red bromobutyl stoppers and sealed with aluminium crimped strips. The product, (1 litre), is diluted 1/10 with clean and adequately oxygenated hatchery water. Aquavac Relera may also be delivered to fish undiluted as a booster vaccine, (0.1ml/fish), subsequent to initial immersion treatment. For booster injection, the vaccine must be administered using a hand-held or automatic multi-dose injection applicator that prevents flush-back. The product is administered by intra-peritoneal injection in the ventral area to fish anaesthetised by a suitable method. The particulars of the containers and controls performed are provided and conform to the regulation.

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

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

The product is a novel pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. There is no monograph for ERM, and therefore standard texts apply. Where appropriate, the monograph for Vibriosis vaccines has been used as an exemplar.

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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substances are inactivated cells of *Yersinia ruckeri* Hagerman type 1 strain, and inactivated cells of *Yersinia ruckeri* EX5 biotype strain. These established substances are not described in the European/British Veterinary Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with the European Pharmacopoeia (Ph.Eur) and the United States Pharmacopeia (U.S.P).

The bacterial master seeds 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/or 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. Tests were performed for appearance, inactivation, sterility, volume of contents, target species safety and potency.

The demonstration of 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

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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. Shelf life for this product is designated as being 2 years as packaged for sale, and vaccine intended for booster injection should be used within 5 hours of broaching the vial.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

On primary vaccination by immersion, the fish must be at least 5g in weight. Fish receiving booster injection must be at least 12g in size. The product is not to be frozen and is to be protected from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal were demonstrated in laboratory trials. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The safety of Aquavac Relera for use in fish, for both the immersion and injection routes was established. All test parameters remained the same for all fish for all tests.

Only healthy fish should be vaccinated, and vaccination should not be performed where the water temperature is below 12$^{o}$C. Administration of the product by injection may cause a very slight adhesion (Speilberg score 1), at the site of injection. These lesions may persist for several weeks, but are normally not observed after 3 months.

The product is not to be administered to broodstock fish, or fish intended as brood stock. In addition, no information is available on safety and efficacy when Aquavac Relera is used with other veterinary medicinal products. Therefore, any decision to use this product before or after other products must be made on a case by case basis.

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

Residual traces of formaldehyde are contained in the product. Such traces are classified in Annex II of the EU Council Regulation 2377/90 (Regulation 2765/95). Based on this information, no withdrawal period is proposed.

Field studies

Two studies were performed to assess the safety and efficacy of the product when used diluted in a tank of fish and as an injection. Minor lesions were observed when the product was given by injection, but these were not considered significant.

Acceptable data was provided which demonstrated that the product was safe for use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was 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. The vaccine is an inactivated bacterial vaccine containing no adjuvant; therefore the components present no risk. Residual levels of formaldehyde remaining in the product from the inactivation procedure are acceptable.

## IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

### *Laboratory Trials*

Laboratory studies were carried out on the target species, rainbow trout. Fish were sourced from a hatchery that is seronagative for antibodies against *Yersinia ruckeri*. Tests to confirm seronegative status were performed on a sample of fish where they were of appropriate size, all results were negative. Each batch of vaccine used in the tests was produced and controlled according to specified Quality Standards. For all holding and vaccination of fish, procedures were carried out at $12^{o}C \pm 0.5^{o}C$.

1. Both vaccine strains used in Aquavac Relera were tested with regard to efficacy against susceptible and EX5 resistant strains of ERM when given by immersion. This was in order to determine the most effective vaccine formulation for the product. A constant amount of Hagerman antigen was used against a varying amount of EX5 antigen. The product was diluted at 1:10 final concentration for delivery to fish and they were immersed in the product for 30 seconds. Three batches of vaccine were tested, and there were 60 fish in each test group, including a negative control group which received no vaccine.

30 fish from each group were challenged with virulent culture at 28 days post-vaccination in order to test the effectiveness of the product. The best formulation produced clinically acceptable relative percentage survival (RPS) values of 85% and 93% in two comparable studies for the EX5 biotype. Immunity to Hagerman Type 1 (RPS value) was previously established for Aquavac ERM, there was therefore no requirement for varying amounts of this antigen to be tested. Vaccine formulation data were elucidated from the results.

2. 3 groups of 30 fish per day were tested with Aquavac Relera over 7, 14 and 28 days, for responses to both virulent challenge cultures. This was done in order to assess the onset of immunity to ERM via the immersion route. The 3 groups comprised one group receiving a full dose of vaccine, one group receiving half the full dose, and a final group receiving no vaccine, (negative control). For the immersion route, onset of immunity was designated as being 336 degree days, (28 days). Use of the product produced clinically acceptable RPS values of 89% for Hagerman Type 1 and 97% for EX5 strains at this endpoint.

3. The duration of immunity provided by Aquavac Relera via the immersion route was tested using full dose, half dose and negative control. 3 groups of 30 fish per group were challenged with both virulent cultures at 3 months and 6 months post-immunisation. Duration of immunity was designated as being 205 days (6 months) at 12$^{o}$C for the Hagerman type 1 strain, and 133 days (4 months) at 12$^{o}$C for the EX5 biotype strain. The protection against the EX5 biotype was found to wane during the indicated period. RPS values were clinically acceptable for both vaccine strains.

4. In order to identify the time required for the development of immunity for booster injection, 30 fish in one full dose group and 30 fish in one negative control group were challenged with both virulent cultures at 21 and 28 days post-inoculation. Immunity was established and was not studied beyond 28 days. RPS values were acceptable.

### *Field Trials*

The applicant has conducted field studies which demonstrate that use of Aquavac Relera (primarily via the immersion route and as a booster vaccine if required), is effective against ERM.

Fish were divided into 3 batches, consisting of two groups each. One group was exposed to Aquavac Relera, and one to the monovalent (Hagerman type 1 only) control vaccine, Aquavac ERM. 186,139 fish were vaccinated by immersion in Aquavac Relera, and 137,820 fish were vaccinated with the monovalent vaccine. Both Vaccines were used at a final concentration of 1:10. The fish were vaccinated at a hatchery, and then transported 14-15 days post-vaccination to a farm. Observations were made on a regular basis, and at 5 time points, after which 30 fish were bacteriologically analysed. Data was supportive of laboratory testing showing that Aquavac Relera was effective in treating ERM via the immersion route. The product is also permitted to be used as a booster injection. RPS values were clinically acceptable.

## 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 risk benefit 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 Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).
This section 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.
None