ANSES

Agence Nationale du Médicament Vétérinaire
(National Agency for Veterinary Drugs)
(Reference Member State)
BP 90203
35302 FOUGERES CEDEX
FRANCE

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Aquavac Vibrio Immersion and Injection

Update 14/11/2016

MODULE 1

PRODUCT SUMMARY

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

EU Procedure number	FR/V/0164/001/MR
Name, strength and pharmaceutical form	Aquavac Vibrio Immersion and Injection
Applicant	Initial: Schering-Plough Vétérinaire 92, rue Baudin 92307 LAVALLOIS-PERRET Cedex France Current : Intervet Rue Olivier de Serres Angers technopole 49070 BEAUCOUZE ; FRANCE
Active substances	• Inactivated cells of *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID, RPS_{60}(*) > 75% • Inactivated cells of *Vibrio ordalii*[1] strain MSC 275, RPS_{60}(*) > 75% *RPS: relative percentage of survival 6 AT 60% of mortality of the controls
ATC Vetcode	ATC Vet code QI10BB01
Target species	Rainbow trout (*Oncorhynchus mykiss*)
Indication for use	Active immunisation to reduce mortality caused by vibriosis due to *Listonella* (*Vibrio*) *anguillarum* serotype I and *Vibrio ordalii*[1]. The onset of immunity is at least 336 degree days. A duration of immunity of 1200 degree days has been shown.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.ircp.anmv.anses.fr/

MODULE 3

[1] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum*
O2

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 procedure	05/07/2006
Date product first authorised in the Reference Member State (MRP only)	12/01/2005
Concerned Member States for original procedure	CY,DK,EL,ES,FI,IE,IT,MT,PT,SI,UK

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 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 *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID, inducing a relative percentage survival in vaccinates, at time of 60% of mortality in controls, after vaccination by injection and subsequent challenge of at least 75%
- Inactivated cells o*f Vibrio ordalii*[2] strain MSC 275, inducing a relative percentage survival in vaccinates, at time of 60% of mortality in controls, after vaccination by injection and subsequent challenge of at least 75%

The product also contains less than 0.5 mg/mL of formaldehyde, residue of the inactivation of the active ingredients.

[2] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum*
O2

The containers consist of 1 litre high density polyethylene containers, with bromobutyl stopper and aluminium sealing ring. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains, formulation, and absence of preservative are justified.

The inactivation process is 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

The product is manufactured 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:
- *Listonella* (*Vibrio*) *anguillarum* strain 78-SKID,
- *Vibrio ordalii*[3] strain MSC 275.

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 European pharmacopoeia monographs where these exist, or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines.

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/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.

[3] *Vibrio ordalii* is a subset of *Listonella* (*Vibrio) anguillarum*
O2

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, volume filled, pH, batch potency test (by challenge), residual formaldehyde content, safety test in target species, sterility, inactivation control.

Batch potency test: Two groups of 60 rainbow trouts each, weighting 4-6 g, are used. One group is injected with 0.1 ml of the vaccine by intraperitoneal route, the other is injected with 0.1 ml of a saline solution. Both groups are maintained for 28 days at 12-15 °C. The fish are then challenged : 30 vaccinates and 30 controls being inoculated with a virulent strain of *V. anguillarum* (VIB 1), 30 vaccinates and 30 controls being inoculated with a virulent strain of *V. ordalii* (VIB 2). The fish are maintained until 60 % specific mortality is reached in the controls. At least 60 % of the control group must die within the 21 days of the death of the first control fish following challenge. The RPS for fish vaccinated by injection must be not less than 75 %, calculated at the time corresponding to 60 % mortality in the controls (RPS = (1 - % vaccinate mortality/% control mortality) x 100).

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

The storage of the antigen prior to formulation was considered acceptable because the potency of the vaccine at release is checked through challenge.

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.

To justify the in-use shelf-life of the broached product, it was shown that the vaccine remains sterile despite broaching on several occasions.

III. SAFETY ASSESSMENT

The vaccine is formulated to a target concentration for both components. It is inactivated and the control of the active ingredients at the level of the final product is performed by a challenge test in the target species.

The concept of maximum potency was not deemed appropriate for this product. It was considered by the RMS that any batch formulated to these target concentrations and with a compliant batch potency test result was appropriate to support the demonstration of the safety of the vaccine.

Laboratory trials

The safety of the administration of one dose and an overdose in the target species is demonstrated in the following studies:

- in rainbow trout (vaccination at 12°C):
    - by immersion
        - pivotal study: in 2g fish at 12°C, 100 fish receiving a normal dose, 100 fish receiving a double dose (dilution 1/50, immersion of 60 seconds) and 100 controls. Observation of 28 days
        - other studies: hundreds fish of 6 to 12g, receiving either a single or a double dose observed for 21 to 28 days, including a study in 12g fish receiving Aquavac Vibrio Oral for revaccination at the size of 14g
    - by intra-peritoneal injection
        - pivotal study: in 6g fish at 12°C, 100 fish receiving a double dose (0.2 ml) and 50 controls observed for 21 days
        - other studies: hundreds fish of 6 to 12g, receiving either a single or a double dose observed for 21 to 28 days Data are also available for the Sea Bass:
- in sea-bass by intra-peritoneal route at 21°C: in 2 different studies, a total of 200 fish between 26 and 37.5g were vaccinated with either a single (0.1 ml) or a double (0.2 ml) dose and observed for 21 to 28 days

The safety of the repeated administration of one dose was not investigated, which is acceptable because the vaccine is intended to be used once in the lifetime of the fish.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

No adverse reaction were observed.
The SPC reflects these results; however, indication for sea bass was not adopted because of lack of demonstration of efficacy in this species (see next chapter).

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

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

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

The adjuvant and excipients used are included in Annex II of the MRL regulation. Based on this information, no withdrawal period is proposed.

The interaction of the vaccine with Aquavac Vibrio Oral was studied. 12g rainbow trout were vaccinated with a single dose of Aquavac Vibrio Immersion and Injection and a revaccination was conducted in the fish at the size of 14g with a single dose of Aquavac Vibrio Oral. No adverse reaction were observed. Efficacy of this protocol was also studied (see next chapter). Therefore, the possible association of both products is indicated in the SPC.

Field studies

About 70,000 rainbow trout of 28.5g were vaccinated by immersion at a temperature of 10-13°C; a revaccination with Aquavac Vibrio Oral was performed 11 weeks later, when the fish were of a size of 83.1g. 110,000 controls were included. No abnormality was seen.

About 53,000 sea bass of 159g were vaccinated by intra-peritoneal injection and 123,000 fish kept as controls. 0.6% of mortality was observed during the first 2 days following vaccination.

Ecotoxicity

The applicant provided an argumentation which showed that no further assessment is required.

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

IV CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show:

- in rainbow trout (vaccination at 12°C):
    - by immersion
        - pivotal study: in 2g fish at 12°C, vaccination of 100 fish and challenge 28 days later of 50 fish with *Vibrio anguillarum* (VIB1) and 50 fish with *Vibrio ordalii* (VIB2); same number of fish included as controls. 100% of the vaccinates survived whereas all the controls died.
        - other studies: hundreds fish of 6 to 12g, receiving a single dose of vaccine were challenged 28 days after vaccination with the same strains. The relative percentage of protection (RPS) was between 73 and 100%.
    - by intra-peritoneal injection
        - pivotal study: in 6g fish at 12°C, vaccination of 100 fish and challenge 28 days later of 50 fish with *Vibrio anguillarum*

(VIB1) and 50 fish with *Vibrio ordalii* (VIB2); same number of fish included as controls. 100% of the vaccinates survived whereas 96% of the controls died.
  - other study: RPS of 80 to 100% in fish vaccinated at the size of 9g and challenged 28 days later
- a single study was performed in sea-bass (vaccinated by intra-peritoneal route at the size of 26g), demonstrating a protection to a Vibrio anguillarum O1 challenge performed 33 days and 89 days after vaccination; the results to a Vibrio angillarum O2alpha challenge could not be interpreted.

Field Trials

The applicant has conducted field studies in about 180,000 rainbow trout (including 70,000 vaccinates) and 176,000 sea bass (including 53,000 vaccinates). As the field challenge could not be objectivated and other vaccines were also administered, the improved results observed in vaccinates cannot be attributed with certainty to Aquavac Vibrio Immersion and Injection.

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.

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.

Quality changes

Summary of change	**Approval date**

Change in primary packaging (addition of supplier of HDPE)	**2012**