FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
8 rue Claude Bourgelat
Parc d'activités de la Grande Marche - Javené
BP 90203
35302 Fougères Cedex
France

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ICTHIOVAC VR/PD

09/06/2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0314/001/DC
Name, strength and pharmaceutical form	ICTHIOVAC VR/PD, emulsion for injection for sea bass
Applicant	Laboratorios Hipra, S.A. Avda. La Selva, 135 Amer (Girona) 17170 Spain
Active substance(s)	*Photobacterium damselae* subsp. *piscicida* DI 21, inactivated *Listonella anguillarum* serotype O1, inactivated *Listonella anguillarum* serotype O2α, inactivated *Listonella anguillarum* serotype O2β, inactivated
ATC Vetcode	QI10X
Target species	Sea bass (*Dicentrarchus labrax*)
Indication for use	For the active immunisation of sea bass to reduce the mortality caused by infection by *Photobacterium damselae* subsp*. piscicida* (pasteurellosis) and by infection by *Listonella anguillarum* serotypes O1, O2α and O2β. Onset of immunity 42 days after vaccination at 19 - 21°C (798 - 882 degree days) Duration of immunity: not established

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	26/04/2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	HR, EL, IT, PT, ES

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.
The CVMP classified this product as falling into the scope of minor species, limited market products (MUMS); the assessment was performed according to the MUMS guideline (EMA/CVMP/IWP/123243/2006-Rev.2, Guideline on Data requirements for Immunological veterinary medicinal products intended for minor use or minor species/limited markets) in force at the time of assessment.
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 *Photobacterium damselae* subsp. *piscicida* DI 21 inducing RPS (relative percentage of survival) of ≥ 60% after an IP (intra-peritoneal) challenge in sea bass.
- inactivated *Listonella anguillarum* serotype O1, inducing RPS of ≥ 75% after an IP challenge in sea bass.
- inactivated *Listonella anguillarum* serotype O2α, inducing RPS of ≥ 75% after an IP challenge in sea bass.
- inactivated *Listonella anguillarum* serotype O2β, inducing RPS of ≥ 75% after an IP challenge in sea bass.

The excipients are montanide, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate and phosphate buffered saline.

The container/closure system consists of high density polyethylene bottles closed with rubber stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strains, formulation, inactivating agent and preservative 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

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 substance *Photobacterium damselae* is an established active substance, the active substances *Listonella anguillarum* are established substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substances specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications have been provided.

Starting materials of non-biological origin used in production comply with relevant pharmacopeia monographs or in-house specifications.

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; 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/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 2 consecutive runs, conforming to the specifications, are provided, in accordance with the MUMS guideline.

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, residual formaldehyde content, sodium methyl parahydroxy-benzoate content, sodium propyl parahydroxybenzoate content, potency test, viscosity, filling volume, emulsion stability and sterility.
The demonstration of the batch to batch consistency is based on the results of 2 batches (compliant to MUMS guideline) produced according to the method described in the dossier.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines (including MUMS guideline), demonstrating the

stability of the product throughout its shelf life when stored under the approved conditions.

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

III. SAFETY ASSESSMENT

All batches used in the safety studies were representative of the production process. The dose to be used was the recommended dose for use; the content in active substances was not maximum, but however standard; this is acceptable according to the MUMS guideline.

Laboratory trials

The safety of the administration of one dose in the target animal is demonstrated in 2 studies. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
Each of the two studies involved equal numbers of vaccinated and control fish (sea bass), vaccinated with a single dose by intraperitoneal (IP) route after anesthesia, the 1st study using fish of a mean weight of 24 g, the 2nd study using fish of a mean weight of 11.4 g. The fish came from populations free from the *L. anguillarum* and *P. damselae*. The vaccination was performed under normal water conditions (20-22°C, seawater salinity).
The fish were observed for 21 days after vaccination for local and general reactions and growth, then euthanised and scored for IP reactions according to the Spielberg scoring system.
There was neither abnormal mortality, nor adverse reactions following vaccination and the fish scored 0 to 1 (adhesion without pigmentation) for IP lesions at necropsy.
The lesions observed and their frequency were reported in the SPC.

The safety of the administration of an overdose was not investigated as Icthiovac VR/PD is an inactivated vaccine, and this testing is not required for inactivated vaccines.

The safety of the repeated administration of one dose was not investigated, as Icthiovac VR/PD is intended for single use only.

No investigation of effect on reproductive performance was conducted therefore an appropriate warning is included in the SPC (section 4.7) that the vaccine is not recommended in breeders.

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

The adjuvant and excipients used are either approved food additives, or listed in annex 1 of Commission Regulation (EU) 37/2010. Based on this information, no withdrawal period is proposed.

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

Field studies

No field study was performed, using Icthiovac VR/PD; this is a possibility allowed by the MUMS guideline.
However, the applicant provided additional representative field safety and efficacy data gathered from fish vaccinated with similar vaccines produced by the applicant, with the same formulation as Icthiovac VR/PD. These data confirmed the safety and efficacy of this formulation under field conditions.

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:

- As the vaccine is inactivated, there is no risk of spread of live organisms,
- The active substances, adjuvants and excipients are not hazardous to animals, humans or the environment.

However, because of the adjuvant, a warning is introduced regarding self-injection.

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)

All batches used in the efficacy studies were representative of the production process. The dose to be used was the recommended dose for use; the content in active substances was not minimum, but however standard; this is acceptable according to the MUMS guideline.

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements.

In two laboratory studies involving more than 500 vaccinated and 500 control fish, the efficacy was demonstrated by an IP challenge in fish of the minimum size, against each of the 4 vaccines strains; the onset of immunity was set at 42 days (delay between vaccination and challenge). The relative percentage of survival was above 60% for the challenges with *Photobacterium damselae*, and above 75% for the challenges with *Listonella anguillarum*.
The duration of immunity has not been established. This was justified by the applicant and clearly reported in the SPC.
The vaccine was not used under field conditions; however, the applicant provided supportive data gained from the use of similar vaccines with the same formulation produced by the same manufacturer. The data show the benefit of the vaccination under field conditions, and this was taken into account to balance the lack of demonstration of the duration of immunity.

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 veterinary Heads of Agencies website (http://www.hma.eu/vmriproductindex.html).

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.

Variation IB001: extension of the shelf-life of the vaccine from 18 to 24 months

Variation IB002: extension of the storage of the 4 antigens from 4 to 12 months.