# Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
**(Reference Member State)**

**DECENTRALISED PROCEDURE**

# [DRAFT] PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## ALPHA DIP Vib concentrate for dip suspension for sea bass

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# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | ES/V/0251/001/DC |
| Name, strength and pharmaceutical form | ALPHA DIP Vib concentrate for dip suspension for sea bass. |
| Applicant | PHARMAQ AS<br>Industrivegen 50<br>7863 Overhalla (Norway) |
| Active substance(s) | Inactivated Listonella anguillarum (Vibrio anguillarum) serotype O1, strain AL 112 |
| ATC Vet code | QI10X |
| Target species | Sea bass (*Dicentrarchus labrax*) |
| Indication for use | For active immunisation of sea bass to reduce mortality and clinical signs caused by infection with *Listonella anguillarum* serotype O1 (vibriosis). |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

# MODULE 3

## PUBLIC ASSESSMENT REPORT

| | |
|---|---|
| Legal basis of original application | Decentralised application in accordance with Article 12.3 of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | D210= 24.02.2016 |
| Date product first authorised in the Reference Member State (MRP only) | N/A |
| Concerned Member States for original procedure | EL, HR, IT and PT |

## I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 *Listonella anguillarum* (*Vibrio anguillarum*) serotype O1, strain AL 112 and as excipients purified water (the vaccine may contain formaldehyde as a residue after inactivation).

The containers are sterile transparent 500 ml or 1000 ml polyethylene terephthalate (PET) bottles with screw cap. The cap is of high density polyethylene (HDPE). The container is tamper-evident.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain and formulation as well as the absence of 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.

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 the inactivated *Listonella anguillarum* serotype O1 antigen. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with pharmacopoeia monographs.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

However, dossier includes risk assessment on the seed *L.anguillarum*, one starting material of animal origin but it is concluded that there is not potential risk of transmission of TSEs.

## E. Control tests during production (immunologicals)

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 general characteristics of the product (appearance, free formaldehyde), identity of the active substance, potency, and sterility.
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.

After dilution or reconstitution according to directions the vaccine should be used immediately

## H. Genetically Modified Organisms

Non applicable.

## J. Other Information

Non applicable.

## III. SAFETY ASSESSMENT

ALPHA DIP Vib is an inactivated vaccine for sea bass against vibriosis. It is intended to protect juveniles in the early on-growing phase of the production cycle (from 1 gram) up to approximately 15 grams.
It has been demonstrated that the basic vaccination scheme is safe for fish used in the trial.

This vaccine is within the scope of the current MUMS guideline (EMA/CVMP/IWP/123243/2006-Rev.2) at day of submission. The laboratory trials have been performed in Sea bass of the recommended weight at vaccination.

The holder has assumed a commitment to provide data from field as a post approval vaccination. The follow up will be performed under commercial conditions until 21 days post second dip vaccination.

**Laboratory trials**

The applicant has presented two studies about an overdose administration and safety of the repeated administration of one dose. This in line with Directive 9/2009/EC and MUMS Guideline.

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 vaccine does not contain excipients other than purified water. The vaccine may contain formaldehyde as a residue after inactivation and it is stated in the SPC. 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.

Special precautions for use in animals and to be taken by the person administering the vaccine to the animals are also included in the SPC. Adverse reactions are not known

The following table shows a summary of the laboratory trials provided in the dossier:

| Study | Type of study | Nº of fish | Results |
|---|---|---|---|
| Safety of an overdose | Observation of mortality and local and systemic reactions | 250 | The vaccine is safe for fish of 1 gram |
| Safety of an overdose | Observation of mortality and local and systemic reactions | 100 | The vaccine is safe for fish of 1 gram |

| | | | |
|---|---|---|---|
| Safety of a dose according to the recommended schedule | Efficacy study but safety was also reported.<br>Observation of mortality and behaviour | 420 | The vaccine is safe according to the recommended schedule. |

**Field studies**

According to MUMS Guideline, if laboratory studies sufficiently show no safety risk, field studies are not required. It should be sufficiently justified that data from the laboratory studies are representative for safety under field conditions. Safety data from the field may be required as a follow-up measure.

The assessment of laboratory studies justifies the absence of field studies.

**Ecotoxicity**

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. EFFICACY

ALPHA DIP Vib is an inactivated vaccine for sea bass against vibriosis. It is intended to protect juveniles in the early on-growing phase of the production cycle up to approximately 15 grams.

ALPHA DIP Vib is claimed for active immunisation of sea bass to reduce mortality and clinical signs caused by infection with *Listonella anguillarum s*erotype O1. The onset of immunity occurs no later than 600 degree days post vaccination.

## IV.B Clinical Studies

The efficacy of the vaccine has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine reduce mortality and clinical signs caused by infection with *Listonella anguillarum s*erotype O1 (vibriosis).

Onset of immunity is established at 600 degree days and duration of immunity has not been established. It is stated in section 4.2 of the SPC. However, the applicant accepts to provide efficacy data from the field as a post approval commitment. The follow-up will be performed under commercial conditions.

***Laboratory trials:***

The laboratory trials have been performed in Sea bass of the recommended weight at vaccination. A preliminary study to investigate the suitable challenge dose was carried out using unvaccinated fish.
The following table shows a summary of the laboratory trials provided in the dossier:

| Study | Type of study | Nº of fish | Results |
|---|---|---|---|
| Efficacy of one dose | Challenge by intraperitoneal route 4 weeks after the vaccination | 240 | Fish vaccinated at 9.6 grams were protected |
| Efficacy according to the recommended schedule | Challenge by intraperitoneal route 4 and 5 weeks after the second dose | 420 | Fish vaccinated according to the recommended schedule were protected |
| Efficacy according to the recommended schedule | Challenge by intraperitoneal route 4 weeks after the second dose | 300 | Fish vaccinated according to the recommended schedule were protected |

***Field Trials***

According to MUMS Guideline, if sufficient laboratory studies are performed, field studies are not required.

## 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 (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.

### Administrative changes

| **Summary of change (Application number)** | **Section updated in Module 3** | **Approval date** |
|---|---|---|
| ES/V/0251/001/II/001: Additional batch potency test site for ALPHA DIP Vib concentrate for dip suspension for the target species sea bass. | II | 27.11.2016 |

### Quality changes

| **Summary of change (Application number)** | **Section updated in Module 3** | **Approval date** |
|---|---|---|
| ES/V/0251/001/IB/003: extend the shelf life of the vaccine to 24 months based on real time data from 27 months stability testing**.** | IB | 28.06.2017 |