DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ALPHA JECT micro 1 Noda

CORREO ELECTRÓNICO

mresvet@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0263/001/DC
Name, strength and pharmaceutical form	ALPHA JECT micro 1 Noda, emulsion for injection for sea bass
Applicant	PHARMAQ AS Harbitzalleen 2A, Oslo 0275 Norway
Active substance(s)	Inactivated Red-spotted Grouper Nervous Necrosis Virus (RGNNV) strain ALV1107 ≥ 0.07 antigenicity units[1] [1] quantity of antigen measured in vaccine (short version AgU)
ATC Vet code	QI10X
Target species	Sea bass (*Dicentrarchus labrax*)
Indication for use	For active immunisation of sea bass to reduce mortality caused by Red-spotted Grouper Nervous Necrosis Virus (RGNNV).

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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: 20/9/2017
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Original CMS (PDC): EL, HR, IT New CMS (RUP-1st wave): FR

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 slight reactions observed are indicated in the SPC.
The product is safe for the user, and for the environment, when used as recommended.
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. Qualitative and quantitative particulars

The vaccine is presented as an emulsion for injection.

Each dose (0.05 ml) of the product contains ≥ 0.07 antigenicity units (quantity of antigen measured in vaccine) of inactivated Red-spotted Grouper Nervous Necrosis Virus (RGNNV) strain ALV1107 as active substance, liquid paraffin (mineral oil) as adjuvant and sorbitan oleate and polysorbate 80 as emulsifiers.

The container is a 250 ml or 500 ml sterile UVO injection bag made of a multilayer plastic foil.

The containers comprise three components: the bag, the giving port with a rubber stopper and the filling tube.
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 is 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 Red-spotted Grouper Nervous Necrosis Virus (RGNNV) strain ALV1107. 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.
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 and Guidelines.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Control tests during production

The tests performed during production are described and according to the MUMS guideline (EMA/CVMP/IWP/123243/2006-Rev.2), results from in-process control tests performed on one R&D batch and one production batch of VNNV antigen are provided.

E. 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, centrifugation, and viscosity), identity and assay of the active substance (potency) and excipients (free formaldehyde), potency, and sterility.
Batch potency test is performed by an “in vitro” method, in line with 3Rs requirements.
The demonstration of the batch to batch consistency is based on the results of two consecutive production runs (R&D batches allowed) according to the MUMS guideline (EMA/CVMP/IWP/123243/2006-Rev.2).
Results from control tests on the finished product for two R&D batches and one production batch, manufactured according to Part 2B of the vaccine module, are provided.

F. 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.
Satisfactory data have been provided to justify a shelf life of 30 months at 2-8°C for the storage of the vaccine.
The in-use shelf-life of the broached vaccine is supported by the data provided. Shelf life after first opening the immediate packaging is 10 hours.

G. Other Information

Non applicable.

III. SAFETY ASSESSMENT

ALPHA JECT micro 1 Noda contains formaldehyde inactivated Red spotted Grouper Necrosis Virus (RGNNV) and it is formulated with a mineral oil adyuvant. It is indicated for the active immunisation of sea bass (*Dicentrarchus labrax*) to reduce mortality caused by Viral Nervous Necrosis (VNN).

The recommended dose volume is 0.05 ml per fish weighing a minimum of 12 g at the time of vaccination.

Six different batches were used for the safety assessment.

Record of the claims of the SPC

- Contraindications: none
- Special warnings for each target species: “Due to handling, vaccination may be followed by temporary reduced appetite”.
- Special precautions for use: standard wording for mineral oil adyuvanted vaccine (section 4.5)
- Adverse reactions (frequency and seriousness): Oil adjuvants are associated with increased risk of local reactions in the form of adhesions in the abdomen and pigmentation on the viscera in fishes.
  Very common (> 1/10):
  - At 12 months, mild abdominal adhesions have been shown in laboratory studies.
  - At 12 months, small amounts of melanin, seen as few spots covering very limited areas of the viscera often close to the injection site have been observed in laboratory studies. “Oil adjuvants are associated with increased risk of local reactions in the form of adhesions in the abdomen and pigmentation on the viscera in fishes.

Laboratory trials

The safety of the administration of one dose in the target animal is demonstrated. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Study	Nº of fish	Type of study	Results
Verify that vaccination does not give positive PCR result.	150		Vaccination does not give positive PCR result.
Standard safety assessment 3 and 6 week post vaccination.	1215	Local reactions post vaccination, mortality, abnormal behaviour and weight was recorded	No mortality and no abnormal behaviour Mild abdominal adhesions Limited melanisation on the viscera.
Standard safety assessment 3 and 6 week post vaccination	585	Local reactions post vaccination, mortality, abnormal behaviour and weight was recorded	No mortality and no abnormal behaviour Mild abdominal adhesions Limited melanisation on

			the viscera.
Primary objective efficacy but long term local reactions assessed (12 months)	218	Local reactions post vaccination, mortality, abnormal behaviour and weight was recorded.	No mortality and no abnormal behaviour Mild abdominal adhesions Limited melanisation on the viscera.
Primary objective efficacy but long term local reactions assessed (6 months).	220	Local reactions post vaccination, mortality, abnormal behaviour and weight was recorded.	No mortality and no abnormal behaviour Mild abdominal adhesions Limited melanisation on the viscera.

No specific overdose study has been performed (it can be omitted according to Ph. Eur 5.2.6. *Evaluation of safety of veterinary vaccines and immunosera*).

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals. The starting materials from which the product is derived is not considered a potential risk factor.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal 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.

No MRL is required for any excipient of the vaccine according to 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

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

Environmental Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

IV. CLINICAL ASSESSMENT (EFFICACY)

ALPHA JECT micro 1 Noda, emulsion for injection for sea bass is an inactivated vaccine for sea bass.

ALPHA JECT micro 1 Noda is claimed for active immunisation of sea bass to reduce mortality caused by infection with Red-spotted Grouper Nervous Necrosis Virus (RGNNV). The onset of immunity occurs at 466 degree days post vaccination and duration of immunity is expected for 1 year.

Sea bass of a minimum weigh of 12 g should be vaccinated with a dose of 0.5 ml by intraperitoneal route. The fish should be anaesthetised prior to injection and it is recommended to starve the fish for a minimum of 24 hours before 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 caused by infection with RGNNV.

Onset of immunity is established at 466 degree days post-vaccination and duration of immunity has been established in 1 year.

Laboratory trials:

The laboratory trials have been performed in Sea bass of the recommended weight at vaccination by the recommended route of administration. 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
Establishment of the challenge dose	After vaccination, challenge with four different isolates and challenge with different dilutions of the choosen isolate	320	Dilutions used in challenge studies should range from 1:50000 to 1:200000
Cross protection	Intramuscular challenge against four different strains	320	Cross protection against the four strains is shown
Efficacy according to the recommended schedule	Intramuscular challenge 6 weeks post-vaccination	600	Fish vaccinated according to the recommended schedule were protected
Efficacy according to the recommended schedule	Intramuscular challenge 6 weeks post-vaccination	500	Fish vaccinated according to the recommended schedule were protected
Efficacy according to the	Intramuscular challenge 5 weeks post-vaccination	200	Fish vaccinated according to the recommended

recommended schedule			schedule were protected
Efficacy according to the recommended schedule	Intramuscular challenge 6 weeks post-vaccination	585	Fish vaccinated according to the recommended schedule were protected
Onset of immunity	Intramuscular challenge 3 weeks post-vaccination	160	Onset of immunity is established at 3 weeks post-vaccination (466 degree days)
Duration of immunity	Intramuscular challenge 51 weeks post-vaccination	203	Duration of immunity established at 1 year vaccination

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.

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change in the shelf life or storage conditions of the finished product. Extension of the shelf life of the finished product. Extension of the shelf life of a biological/immunological medicinal product in accordance with an approved stability protocol. (ES/V/0263/IB/001/G)	II.F.	21/09/2018