DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ALPHA JECT micro 2000
emulsion for injection for sea bass

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0306/001/DC
Name, strength and pharmaceutical form	ALPHA JECT micro 2000 emulsion for injection for sea bass
Applicant	PHARMAQ AS Skogmo Industriomrade, Industrivegen 50 7863 Overhalla Norway
Active substance(s)	Inactivated Vibrio (Listonella) anguillarum serotype O1, strain AL 112 ≥ 2.5 antigenicity units[1] Inactivated Photobacterium damselae subsp. piscicida, strain AL 5051 titre[2] ≥9.6 log2 [1] quantity of antigen measured in vaccine (short version AgU) [2] serological response in sea bass
ATC Vet code	QI10X
Target species	Sea bass (*Dicentrarchus labrax*)
Indication for use	For active immunisation of sea bass to reduce mortality of vibriosis caused by Vibrio anguillarum O1 and of pasteurellosis caused by Photobacterium damselae subsp. piscicida.

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: 30/06/2021
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	EL, FR, HR, IT

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 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. Qualitative and quantitative particulars

The product contains inactivated *Vibrio* (*Listonella*) *anguillarum* serotype O1, strain AL, 112 (≥ 2.5 antigenicity units) and inactivated *Photobacterium damselae* subsp. *piscicida*, strain AL 5051 (≥ 9.6 $\log_2$ antibody serological assay in vaccinated Sea bass) and also contains paraffin, light liquid (mineral oil) as adjuvant.

The container/closure system consists of Injection bags made of a multilayer plastic foil with inner layer of ethylene vinyl acetate. The giving port is closed with a bromobutyl rubber stopper.

The choice of the adjuvant, vaccine strain, formulation, inactivating methods and 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.

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

C. Control of Starting Materials

The active substances are inactivated *Vibrio* (*Listonella*) *anguillarum* serotype O1, strain AL, 112 and inactivated *Photobacterium damselae* subsp. *piscicida*, strain AL 5051. They are manufactured in accordance with the principles of good manufacturing practice.

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

Scientific data 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.

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

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.

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 appearance, centrifugation assay, viscosity assay, free formaldehyde, identification and potency for both active substances, identification and assay of the oil adjuvant and sterility.

F. Batch-to-batch consistency

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. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substances (both antigens) 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.

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

III. SAFETY ASSESSMENT

Two batches containing the same composition as the one described in the dossier and two batches containing non-target antigen concentrations were used. These last batches were not used to assess the safety of the vaccine but were included for a complete overview of the vaccine, as support of the pivotal studies (since they contained a higher concentration than the standard one).

Laboratory trials

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

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals and the starting materials from which the product is derived are not considered a potential risk factor. Appropriate warning was included in the SPC.

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 in the vaccine have been evaluated for food safety by the CVMP. According to Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits (MRL) in foodstuffs of animal origin, all substances in the vaccines are classified as allowed substances and therefore no MRLs are required. 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

In the EU, immunologicals veterinary medicinal products for European sea bass is classified as minor use or minor species/limited markets. According to Guideline on requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMEA/CVMP/IWP/123243/2006), demonstrating safety in field studies are not mandatory if laboratory studies sufficiently show no safety risk.

Environmental Assessment

The applicant has 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 it is not likely that the environment will be exposed to significant emission of ALPHA Ject micro 2000. The very limited environmental exposure caused by commercial use of the product does not pose any risk to the

environment. It is recommended that any surplus or out-of-date products are disposed in accordance with local requirements and this is stated in the SPC.

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)

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted dose determination and confirmation studies of efficacy, onset of immunity and duration of immunity, according to relevant guidelines and Ph. Eur. texts.

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine confers active immunisation to Sea bass to reduce mortality of vibriosis caused by *Vibrio anguillarum* O1 and pasteurellosis caused by *Photobacterium damselae* subsp. *piscicida*. Relative percentage survival was above 75% for *V. anguillarum*, and above 60% for *P. damselae*. Efficacy studies were used to obtain safety data too.

Study no.	Efficacy parameter studied	Type of study	No. of fish (total in the study)
1	Dose-response	Intramuscular and immersion challenge against photobacterium (Supportive study)	1460
2	Dose-response	Intramuscular and immersion challenge against photobacterium (Supportive study)	1318
3	Dose-response	Intramuscular challenge against vibriosis (Supportive study)	197
4	Influence of the storage in the efficacy of the vaccine	Intramuscular and immersion challenge against photobacteriosis and vibriosis (Supportive study)	805
5	Onset of immunity	Intramuscular and immersion challenge against photobacteriosis and vibriosis (Pivotal study)	706
6	Duration of immunity	Intramuscular challenge against photobacteriosis and vibriosis (Pivotal study)	1359

Common characteristic of all the laboratory studies::

- Sanitary status of the fish used: unvaccinated fish with a valid health certificate.
- Different groups of fish (vaccinated and control) were used.
- Vaccine rout of administration: intraperitoneal.
- Follow up after the challenge: mortality in vaccinated and control group. Weight was also followed in a sample of every group of fish.

For demonstrating the efficacy of the vaccine, controlled laboratory challenge studies by intramuscular and immersion infection with strains coming from natural

outbreaks were performed. Fish used were unvaccinated, free from disease and a health certificate was provided. Vaccination was performed according to the SPC: injection by intraperitoneal route with a 0.05 ml dose in fish of minimum weight of 12 g.

The onset of immunity was showed in a challenge study carried out with 706 fish. Three fish group were vaccinated with the same batch at 3 separate time points: weeks 0, 2 and 3. Challenge of vaccinated fish against *V. anguillarum* was performed 5 weeks (36 days) post first vaccination, corresponding to a minimum immunisation period of 15 days (2 weeks). All vaccinated groups were significantly protected compared to the control group. Challenge of vaccinated fish against *P. damselae* was performed 6 weeks post first vaccination corresponding to a minimum immunization period of 23 days (approximately 3 weeks). Onset of immunity for *V. anguillarum* was demonstrated at week 2 post vaccination (15 days) and onset of immunity for *P. damselae* was demonstrated at week 3 post vaccination (23 days).

The duration of immunity was showed with one group of fish vaccinated with the vaccine manufactured as described in the dossier with the target concentrations of both antigens. . In relation to *V. anguillarum*, satisfactory results were obtained at 6 and 9 months post-vaccination and the duration of immunity could be established at 9 months post-vaccination. Duration of immunity for *P. damselae* could be established at 3 months post-vaccinationsince the mortality in the vaccinated group was statistically significant in relation to control group. .

Field Trials

In the EU, immunologicals veterinary medicinal products for European sea bass are classified as minor use or minor species/limited markets. According to *Guideline on requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets* (EMEA/CVMP/IWP/123243/2006), demonstrating efficacy in field studies is not mandatory if laboratory studies are sufficient to demonstrate efficacy.

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).

None