MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ALPHA JECT 2000 emulsion for injection for sea bass

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0316/001/MR
Name, strength and pharmaceutical form	ALPHA JECT 2000 emulsion for injection for Sea bass
Applicant	PHARMAQ AS Skogmo Industriområde Industrivegen 50 7863 Overhalla Norway
Active substance(s)	Inactivated *Listonella anguillarum* (*Vibrio anguillarum)* serotype O1, strain AL 112 RPS[1] ≥ 75 Inactivated *Photobacterium damselae* subsp. *piscicida*, strain AL 5051 RPS[2] ≥ 60
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 *Vibrio anguillarum* serotype O1 (vibriosis) and *Photobacterium damselae* subsp. *piscicida* (pasteurellosis). Onset of immunity: 4 weeks at 20 ºC (560 degree days). Duration of immunity: 3 months at 22 ºC (1.980 degree days)**.**

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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	Mutual Recognition application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	13/03/2019
Date product first authorised in the Reference Member State (MRP only)	05/04/2018
Concerned Member States for original procedure	HR

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 slight reactions observed, related to the oil adjuvant are indicated in the SPC.
The product is safe for the user, 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 *Listonella anguillarum* (*Vibrio anguillarum)* serotype O1, strain AL 112 (RPS ≥ 75) and Inactivated *Photobacterium damselae* subsp. *piscicida*, strain AL 5051 (RPS ≥ 60). The adjuvant used is liquid paraffin (mineral oil)

High density polyethylene (HDPE) bottles of 500 mL closed with rubber stopper and aluminium cap are used as containers.
The choice of the adjuvant, vaccine strain, potency, inactivating agent and the absence of preservative are justified.

The inactivation process for both strains and the detection limits 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.

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

C. Control of Starting Materials

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

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

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

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia 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 relevant Ph. Eur. monographs and Guidelines; 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. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, 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 the general characteristics of the finished product (appearance, centrifugation, viscosity and free formaldehyde), potency of both active ingredients and sterility of the final product.

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.

F. Stability

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.

G. Other Information

Non applicable.

III. SAFETY ASSESSMENT

ALPHA JECT 2000 emulsion for injection is an inactivated vaccine intended for active immunisation of sea bass to reduce mortality and clinical signs of vibriosis caused by *Vibrio anguillarum* serotype O1 and pasteurellosis caused by *Photobacterium damselae* subs. *piscicida*. The inactivation is carried out with formaldehyde and the pharmaceutical form is an emulsion for injection. The finished product contains liquid paraffin (mineral oil).

It is recommended for use in sea bass and 0.1 ml of the vaccine should be administered by intraperitoneal route in fish of a minimum weight of 15 grams. Prior to the injection, fish should be anesthetised and it is recommended to starve the fish before 24 hours prior to the vaccination. The vaccine should be well shaken prior to use.

The appropriate use of the vaccine induces adverse reactions: up to 16 months very commonly, fish may exhibit local reactions to the vaccine (mild, with average Spielberg score ≤ 1.5) and very rarely, adhesions (corresponding to a Spielberg score ≥ 3) can be observed.

According to the SPC, to reduce the risk of adverse reactions it is important to deposit the entire dose in the abdominal cavity. The injection needle used should have appropriate length to penetrate the abdominal wall by 1 – 2 mm. The entire needle should be inserted into the midline about one, to one and a half pelvic fin length posterior to the base of the pelvic fin. Prior to the administration, the vaccine should be left to slowly reach 15-20°C by keeping it at room temperature and it is recommended to anesthetize the fish prior to the injection and to starve the fish for a minimum of 24 hours before administration.

The following is a summary of the studies provided in support of the safety of the vaccine:

Study	Number of fish	Type of study	Results
Safety of the recommended dose with two different batches of vaccine	150	Study of local and general reactions 21 days post vaccination. Mortality, behaviour and weight were also recorded	No abnormal behavior or mortality was observed. As it was expected, the levels of vaccine residues were low and the SPC will contain the appropriate warnings.
Safety of double dose according to Ph. Eur.	50	Study of local and general reactions 21 days post vaccination. Mortality, behaviour and weight were also recorded	No abnormal behavior or mortality was observed. As it was expected, the levels of vaccine residues were low and the SPC will contain the appropriate warnings.
Safety of the vaccine according to the recommended dose	935	Study of local reactions at a commercial stage (30 weeks post vaccination)	Disease outbreaks were not recorded during the study. No abnormal behavior was observed. An acceptable level of side effect was recorded

Laboratory trials

The safety of the administration of one dose and a double dose in the target animal is demonstrated in laboratory trials during 21 days post vaccination with fish vaccinated at the recommended weight. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Record of the claims of the SPC

- Contraindications: none
- Special warnings for each target species: Due to handling stress, vaccination may be followed by temporary reduced appetite. Vaccinate healthy animals only.
- 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 adverse reactions in the form of visceral adhesions and pigmentation in the abdomen.

  Very common (>1/10):
  - Up to 16 months post vaccination mild adhesions are observed, often close to the injection site.

  - Up to 16 months post vaccination small amount of melanin, seen as spots covering very limited areas of the viscera have been observed.

The safety of the veterinary medicinal product has not been established for use in broodstock, and vaccination of broodstock should be subject to a risk benefit evaluation of the prescribing veterinarian.

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 Council Regulation (EEC) 2377/90/EEC or not falling within the scope of Regulation 470/2009/EC. So, no MRL is required. Based on this information, no withdrawal period is proposed.

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. Nevertheless, an observational study up to 30 weeks was performed for examination of local reactions and vaccine residues. This study supported the safe profile of ALPHA JECT 2000.

Environmental Assessment

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)

ALPHA JECT 2000 is an inactivated vaccine. The basic vaccination scheme for sea bass (*Dicentrarchus labrax*) consists of one single dose of 0.1 ml per fish of a minimum weight of 15 grams by intraperitoneal injection.

ALPHA JECT 2000 is claimed for active immunisation of sea bass to reduce mortality and clinical signs caused by *Vibrio (Listonella) anguillarum* serotype O1 and *Photobacterium damselae* subsp. *piscicida* (pasteurellosis).

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 *Vibrio (Listonella) anguillarum* serotype O1 and *Photobacterium damselae* subsp. *piscicida* (pasteurellosis).

Onset of immunity is established at 560 degree days (four weeks at 20ºC) post vaccination and duration of immunity at 3 months at 22ºC.

Laboratory Trials

The laboratory trials have been performed in Sea bass of the recommended weight at vaccination by the recommended route of administration.

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

Study	Number of fish	Type of study	Results
Efficacy	140 70 vaccinated and 70 control	Challenge by intraperitoneal route 5 weeks post-vaccination at 20 ºC	Results support an onset of immunity at 560 degree days (four weeks at 20ºC).
Batch potency test and onset of immunity (three batches)	32 vaccinated and 32 control/ each batch	Challenge by intraperitoneal route 4 weeks post-vaccination at 20ºC	Satisfactory results for *V. anguillarum* and *P. damselae*
Duration of immunity	640 320 vaccinated and 320 control	Challenge by intraperitoneal route 3 months post-vaccination (40 vaccinated and 40 control)	Results support a duration of immunity of at least 3 months post-vaccination at 22ºC for *V. anguillarum* and *P. damselae*

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.