MINISTERIO
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E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España

(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ICTHIOVAC-PD PASTEURELOSIS DORADA

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0215/001/MR
Name, strength and pharmaceutical form	ICTHIOVAC-PD PASTEURELOSIS DORADA RPS≥60% (*) (*) RPS: Relative Percentage of Survival after intraperitoneal challenge in gilthead Concentrate for dip suspension
Applicant	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135,17170 Amer (Girona) SPAIN
Active substance(s)	Inactivated *Photobacterium damselae* subsp. *piscicida*strains DI 21 and It-1
ATC Vetcode	QI10X
Target species	Gilthead (*Sparus aurata*).
Indication for use	For active immunization of gilthead to reduce the mortality caused by infection by *Photobacterium damselae,* subsp. *piscicida* (Pasteurellosis).

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 procedure	Day 90: 22/07/2015
Date product first authorised in the ReferenceMemberState (MRP only)	16/7/2002
Concerned Member States for original procedure	PT, IT, FR, EL, 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 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. Composition

The product contains:

Active substance:
Inactivated *Photobacterium damselae* subsp. *piscicida* strains DI 21 and It-1……RPS ≥60% (*)

(*) RPS: Relative Percentage of Survival after intraperitoneal challenge in gilthead

Excipient:
Culture media

The container consists of 1000 ml of polypropylene bottles, rubber stoppers and aluminium caps.The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain and the inactivating agent are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an establishedpharmaceutical 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

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs and in-house specifications. Two starting materials comply with the USP.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines.

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 3 consecutive runs, conforming to the specifications, are provided.

The tests include purity, identity,viable bacteria count, optical density, inactivationand sterility.

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 fill volume, appearance, pH, residual formaldehyde,, sterility, batch potency and conditioning.

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 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 2 years 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 that determined to be used immediately.

III. SAFETY ASSESSMENT

Three different vaccine batches were used

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated 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. In the SPC it is stated that: “Adverse reaction: None”.

In study**PE-1999-CB-034** a single dose of vaccine ICTHIOVAC-PD was administered to 300 gilthead (0.05-2g) by **dip immersion for one minute**(not overpassing 0.5 Kg of fish per litre)at a temperature of 20-23ºC**.**
Dose: 1:20 vaccine seawater, equivalent to the usage of the vaccinal bath 20 times.

Three batches of the vaccine were used, each one tested in 100 fishes. One hundred additional gilthead was kept as control group.

Fish were observed daily from D-2 to D+28. The parameters evaluated were anorexia, abnormal swimming behaviour, abnormal external appearance and death, as well as the weight evolution.

Results:
- Fishes vaccinated with the different batches of vaccinehad a similar increase in their mean weight evolution (from day 0 to 28) to control animals.
- No abnormal external appearance, anorexia, abnormal swimming behaviour was observed from D0 to D28.

In study **PE-1999-CB-061**a single dose of vaccine ICTHIOVAC-PD was administered to 300 gilthead (0.05-2g) by **bath immersion** method according to the administration recommendations (1:500) (vaccine:water), for **one hour** at a temperature of 20-23ºC.

Three batches of vaccine were used, each one tested in 100 fishes. One hundred additional gilthead was kept as control fishes.

Fish were observed daily up to 28 days after vaccination. The parameters evaluated were anorexia, abnormal swimming behaviour, abnormal external appearance and death, as well as the weight evolution.

Results:
- Fishes vaccinated with the different batches of vaccine had a similar increase in their mean weight evolution (from day 0 to 28) to control animals.
- No abnormal external appearance, anorexia, abnormal swimming behaviour was observed from D0 to D28.

Study **PE-1999-CB-062** was carried out in 200 gilthead distributed in four groups of 50 fishes of the minimum recommended size (0.05-2g). Three groups were vaccinated by **dip immersion** at a temperature of 16ºC Three batches of vaccine were used, each one tested in 50 fishes. They were inoculated with an **overdose** consisting of a vaccine dilution 1:5 (vaccine:water, which constitutes twice the recommended dilution for dip

immersion), for **2 minutes** (twice the recommended time). One group of 50 fishes was kept as control group.

The observation period was of 14 days post administration of the overdose. The parameters evaluated were anorexia, abnormal swimming behavior, abnormal external appearance and death, as well as the weight evolution.

14 days after the inoculation of one overdose, the 150 vaccinated gilthead were revaccinated with a single dose, by dip immersion following the recommendations for vaccine administration (1:10 (vaccine: water), for 1 minute), and by using the three same vaccine batches. Also a mock-vaccinated control group was used. The animals were observed up to 21 days.

Results

- No significant differences were recorded in weight evolution, between the fishes vaccinated and non-vaccinated.
- No abnormal external appearance, anorexia, abnormal swimming behaviour was observed in the trial from D0 to D35.

Study **PE-1999-CB-063** was carried out in 200 gilthead distributed in four groups of 50 fishes of the minimum recommended size (0.05-2g). Three groups were vaccinated by **bath immersion** at a temperature of 16ºC Three batches of vaccine were used, each one tested in 50 fishes. They were inoculated with an overdose consisting of a vaccine dilution 1:250 (vaccine: water, twice the dilution recommended for bath immersion), for **2 hours** (twice the recommended time). One group of 50 fishes was kept as control group.

The observation period was of 14 days post administration of the overdose. The parameters evaluated were anorexia, abnormal swimming behavior, abnormal external appearance and death, as well as the weight evolution.

14 days after the inoculation of one overdose, the 150 vaccinated gilthead were revaccinated with a single dose, by bath immersion (1:500 (vaccine:water) for **1 hour**). The three same batches of the vaccine were tested. The observation period was 21 days post-revaccination and the parameters evaluated were same as previous studies.

Results

- No significant differences were recorded in weight evolution, between the fishes vaccinated and non-vaccinated.
- No abnormal external appearance, anorexia, abnormal swimming behaviour was observed in the trial from D0 to D35.

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 withdrawal period stated in the SPC is zero degree days.

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

As indicated at Guideline on Data requirements for Immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMA/CVMP/IWP/123243/2006-Rev.2), the field studies can cover safety and efficacy in one trial.

Two field trials, referenced as **EC-2000-DI-001** and **EC-ICTHIOVAC-PD-2003-001** were carried out. See IV efficacy

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 no warnings are therefore required.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that this vaccine reduces mortality caused by infection by *Photobacterium damselae,* subsp. *piscicida* (Pasteurellosis).

In the study **PE-1999-CB-034,**four hundred gilthead (0.05-2g) were split in four groups. Groups 1, 2 and 3 were vaccinated by **dip immersion for one minute**(diluting the vaccine 1:20 in seawater) at a temperature of 20-23ºC**,** using three different batches of vaccine. One group of one hundred gilthead (group 4) was kept as mock-vaccinated control group.

All four groups were challenged intraperitoneally at day 28 post-vaccination, and fish were observed for further 28 days.

The assessment of efficacy of the vaccine was calculated following the RPS (Relative Percentage of Survival).

Results:

- No abnormal external appearance, anorexia or abnormal swimming behaviour wasobserved in the vaccinated or unvaccinated fishes.
- No differences were observed in the weight between the four groups.
- RPS and specific mortality met the required established specifications. Results were the following: 85%RPS in group 1, 90% in group 2 and 89% in group 3. The mortality in control group was 60%. It was considered that vaccination with ICTHIOVAC-PD Pasteurelosis is an efficacious method in preventing death by *Photobacterium damselae,* subsp. *piscicida* (Pasteurellosis).

In the study**PE-1999-CB-061,**four hundred gilthead (0.05-2g) were split in four groups. Groups 1, 2 and 3 were vaccinated by **bath immersion for one hour** (dilution 1:500 in seawater) at a temperature of 20-23ºC**,** using three different batches of vaccine. One group of one hundred gilthead (group 4) was kept as mock-vaccinated control group.

All four groups were challenged intraperitoneally at day 28 post-vaccination, and fish were observed for further 21 days.

The assessment of efficacy of the vaccine was calculated following the RPS (Relative Percentage of Survival).

Results:

- No abnormal external appearance, anorexia or abnormal swimming behaviour wasobserved in the vaccinated or unvaccinated fishes.
- No differences were observed in the weight between the four groups.
- RPS and specific mortality met the required established specifications. Results were the following: 81% RPS in group 1, 76% in group 2 and 78% in group 3. The mortality in control group was 62%. It was considered that vaccination with

ICTHIOVAC-PD Pasteurelosis is an efficacious method in preventing death by *Photobacterium damselae,* subsp. *piscicida* (Pasteurellosis).

Duration of the immunity:

In the laboratory study**PE-1999-CB-038,** 300 gilthead were vaccinated by **bath immersion for one hour** in a vaccination solution prepared in a dilution 1:500 (vaccine:water) at 16ºC and 100 were kept as mock-vaccinated. Three batches of vaccine were used.

Five months (150 days) after the vaccination, the control and the vaccinated gilthead were challenged by intraperitoneal injection (0.1 ml/fish of a suspension of two virulent strains of *Photobacterium damselae* subsp. *piscicida* (B.32 and 666)).

Results

- No abnormal external appearance, anorexia or abnormal swimming behaviour was observed in the fishes, neither vaccinated or control (unvaccinated).
- No significant differences were recorded in weight evolution, between the fishes vaccinated and non-vaccinated.
- RPS and specific mortality met the required established specifications. Results were the following: 77.8% RPS in group 1, 72.3% in group 2 and 72.3% in group 3. The mortality in control group was 18% (it is lower than the percentage expected but it is more difficult to reproduce experimental infection in older fish).

It can be concluded that the onset of immunity is 28 days and the duration of immunity is 5 months from vaccination, covering the entire growth period of gilthead.

No study for duration of immunity has been performed by dip immersion. Taking into account that is a “well established and used vaccine” and that is a MUMS, it is acceptable.

Field Trials

The applicant has conducted two field studies to assess both the safety and the efficacy. However, the efficacy was only demonstrated in trial EC-ICTHIOVAC-PD-2003-001, since only in this trial an outbreak occurred.

Study**EC-Icthiovac-PD-2003-001**was performed in farms (hatchery and nursery) located in the north-west area of Spain,with problems associated to pasteurelosis.

20.000 gilthead (*Sparus aurata*) previously unvaccinated against pasteurellosis and with a weight interval 1-2 g were used in this trial (10.000 were vaccinated and 10000 as control group).

Vaccination: Immersion bath for 60 minutes, diluting 1 litre of vaccine in 500 litres of sea water.

From this trial it is concluded:

- No severe reaction attributable to vaccine administration was detected in any of the tanks.
- Fish behaviour, external appearance and appetite were normal and there were no differences of any type with the control group after vaccination.
- There were no significant differences in weight between groups.

- Thesurvival rate in the vaccinated group is 72.7% (RPS)
- Specific mortality rate due to pasteurellosis in the control group (84%) was significantly higher ($p < 0.01$) than in the vaccinated group (23%).

Study **EC-DI-2000-001** was performed in farms (hatchery and nursery) located in the north-west area of Spain, with problems associated to Pasteurelosis.

509.000 gilthead (*Sparus aurata*) previously unvaccinated against pasteurellosis and with a weight 0.05 g were used in this trial (310.000 were vaccinated and 280.000 as control group).

Vaccination: Immersion bath for 60 minutes, diluting 1 litre of vaccine in 500 litres of sea water.

From this trial it is concluded:

- No adverse effects were recorded after vaccination or over the course of the trial.
- Fish behaviour, external appearance and appetite were normal and there were no differences of any type with the control group after vaccination.
- There were no significant differences in weight between groups.
- The efficacy could not be confirmed, as no outbreak of pasteurellosis appeared in the course of the trial.

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).