IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

AquaVac PD3 Emulsion for Injection

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0339/001/DC
Name, strength and pharmaceutical form	AquaVac PD3 Emulsion for injection, for Atlantic salmon
Active substance(s)	Salmon pancreas disease virus (SPDV)strain F93-125, 75% RPP[1] Infectious pancreatic necrosis virus (IPNV), 1.5 ELISA units[2] *Aeromonas salmonicida* subsp. *salmonicida*, 80% RPS_{60}[3] [1]RPP: relative percentage protection in a laboratory test in Atlantic salmon [2]Antigenic mass measured in the final product [3]RPS: relative percentage survival at 60% control mortality in a laboratory test in Atlantic salmon
Applicant	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands
Legal basis of application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	25.02.2015
Target species	Atlantic salmon (*Salmo salar* L)
Indication for use	For active immunisation of Atlantic salmon to reduce clinical signs (heart lesions and pancreas lesions),viremia, viral shedding and mortality from infection with SPDV (Pancreas disease) and to reduce mortality from infections with IPNV (Infectious pancreatic necrosis) and *Aeromonas salmonicida* subsp. *salmonicida* (furunculosis).
ATCvet code	QI10AL
Concerned Member States	UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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, 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains three inactivated antigens: Salmon pancreas disease virus (SPDV), Infectious pancreatic necrosis virus (IPNV) and *Aeromonas salmonicida* subsp. *salmonicida* and the excipients Light liquid paraffin, Sorbitan monooleate, Polysorbate 80 and Phosphate buffered saline.
The container/closure system is bottles of polyethylene terephthalate (PET) closed with a rubber stopper and aluminium cap.

The choice of the adjuvant, vaccine strain, formulation, inactivating agent 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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance (Salmon pancreas disease virus (SPDV), Infectious pancreatic necrosis virus (IPNV) and *Aeromonas salmonicida* subsp. *Salmonicida)* is a novel active substance. The active substance is manufactured 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 has been provided.

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

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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.

D. Control Tests During Production

The tests performed during production are described and the results of 3 production scale size batches for each active substance 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 physical tests (appearance, accelerated stability, type of emulsion and viscosity) as well as tests for identity and potency, free formaldehyde and sterility testing according to the relevant Ph. Eur. monograph.

The demonstration of the batch to batch consistency is based on the results of 3 small scale and 2 production scale size 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 active substances has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (15 months) when stored under the approved conditions.

The in-use shelf-life of the broached vaccine (use within 1 working day) is supported by the data provided.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Introduction and general requirements

All batches used in the safety studies were representative of the production process. While the concentration of the *A. salmonicida* and IPNV antigens are fixed, the SPDV component may be formulated in a range and therefore the maximum

titre was investigated within the pivotal safety studies. Safety data from the larger combination vaccine AquaVac PD7 was also used to support the safety of the smaller combination vaccine AquaVac PD3 and this was considered to be an acceptable approach in accordance with current guidance.

Studies were performed in accordance with the requirements of Directive 2001/82/EC, as amended, the relevant guidelines, and the Ph. Eur. monograph 1521: Furunculosis vaccine (inactivated, oil-adjuvanted, injectable) for salmonids.

III.B Laboratory trials

The safety of the administration of one dose and of an overdose in the target species (Atlantic salmon from 30 gram weight) were investigated in well-conducted laboratory studies, including a GLP-compliant study. As the investigation of the safety of an overdose administration of inactivated vaccines is no longer a requirement of Directive 2001/82/EC, as amended, it can be considered that the overdose study represents a worst case scenario for the safety investigations. AquaVac PD3 is recommended for use as a single administration only, therefore studies designed to investigate the safety of the repeated administration of one dose are not required.

Adverse reactions following vaccination were limited to reactions at the site of injection. Melanisation and vaccine residues are very commonly observed in the abdominal cavity. Light to moderate visceral adhesions (corresponding to Speilberg scores 1 – 3) are very commonly observed, while the occurrence of major adhesions (Speilberg score of 4) is uncommon. No other adverse reactions were observed following vaccination. No additional reactions were observed after an overdose compared to a single dose administration however more vaccine residues can be observed. The adverse reactions are adequately described in the SPC.

Examination of reproductive performance

The safety of the product in fish used for reproduction has not been investigated. Therefore a suitable warning is included in the SPC to contraindicate use of the vaccine in broodstock.

Examination of immunological function

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.

Special requirements for live vaccines

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

User safety

The main risk presented to the user administering the vaccine is that of accidental self-injection. Given that the vaccine contains mineral oil, the worst case scenario arising from accidental self-injection is necrosis and loss of all or part of a finger. However, appropriate risk mitigation measures are included in the product literature and it is not uncommon for veterinary vaccines to contain mineral oil as an adjuvant. Thus, provided that the product is used in accordance with recommendations, it can be concluded that use of the vaccine does not present an unacceptable risk to the user.

Study of residues

The adjuvant and excipients used are either listed in Commission Regulation (EU) No. 37/2010 in Annex I (Allowed substances) for which no maximum residue limit (MRL) is required or else are approved food additives. Formaldehyde is present in the vaccine at 0.05% as a remnant from the inactivation process and is below the limit specified by Ph. Eur.

0062. Thus, the product does not contain any components in quantities that could represent a risk to consumer health that would necessitate a withdrawal period. Based on this information, no withdrawal period is proposed.

Interactions

No specific assessment of the interaction of this product with any other veterinary medicinal product was made. Therefore, an appropriate warning in the SPC is included.

III.C Field studies

One GCP-standard, combined safety and efficacy field study conducted at two locations in the EU was performed involving vaccination of Atlantic salmon pre-smolts with AquaVac PD3. The results of the field study reflected those obtained in the laboratory studies; adhesions in the abdominal cavity were observed at slaughter, however the nature of the adhesions are considered acceptable and such adhesions are commonly observed following administration of inactivated fish vaccines by intraperitoneal injection.
In addition, a further GCP-standard, combined safety and efficacy field study at a different European location involving vaccination of Atlantic salmon with the larger combination vaccine AquaVac PD7 (which contains the same antigenic components and adjuvant as AquaVac PD3, however AquaVac PD7 contains additional antigenic components) was presented in support of the safety in the field. This approach was considered acceptable in accordance with the principles of the Guideline on the requirements for combined vaccines and associations of IVMPs (EMA/CVMP/IWP/59418/2010). The data from this field study are also supportive of those obtained under laboratory conditions for AquaVac PD3.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with relevant guidance which showed that no further assessment is required. The assessment concluded that there is a very low risk to the environment associated with use of the vaccine; AquaVac PD3 contains three inactivated antigens, and none of the other components included in the vaccine formulation are considered to be harmful or would be expected to pose any risk to the environment. No specific warnings are therefore required; the standard disposal advice for inactivated veterinary vaccines is included on the SPC and product literature.
Therefore, 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.A General requirements

The choice of vaccine strains for each of the antigenic components has been shown to be relevant to the current epidemiological situation in the EU.

IV.B Laboratory trials

The efficacy of the product has been demonstrated in several laboratory challenge studies conducted in the target species, in accordance with the recommended vaccination schedule. While the concentration of the *A. salmonicida* and IPNV antigens are fixed, the SPDV component may be formulated in a range and therefore the minimum titre was investigated within the efficacy studies. Efficacy data from the larger combination vaccine AquaVac PD7 was also used to support the efficacy of the smaller combination vaccine AquaVac PD3 and this was considered to be an acceptable approach in accordance with current guidance.
The efficacy of the *A. salmonicida* component of the vaccine was demonstrated in accordance with the immunogenicity requirements of the Ph. Eur. monograph 1521. No specific Ph. Eur. monographs have been elaborated for SPDV or IPNV;

the efficacy of the SPDV and IPNV components of the vaccine was demonstrated according to current Directive requirements and guidance. The study data support the claims:

Reduction of clinical signs (heart lesions and pancreas lesions), viremia, viral shedding and mortality due to infection with SPDV (Pancreas disease)

Reduction of mortality from infections with IPNV (Infectious pancreatic necrosis) and *Aeromonas salmonicida* subsp. *salmonicida* (furunculosis).

The onset of immunity has been established as 500 degree days after vaccination for SPDV and *Aeromonas salmonicida* and 540 degree days after vaccination for IPNV.

The duration of immunity has been demonstrated at 15 months post vaccination for SPDV and at 16 months post vaccination for *Aeromonas salmonicida*. Protection against mortality due to IPNV infection has been demonstrated at 4 months post vaccination in the field.

IV.B Field trials

The applicant conducted one GCP-standard, positively-controlled, combined safety and efficacy field trial including commercial fish farms from two EU member states which were historically affected by the pathogens against which protection is claimed. Although there were no clinical outbreaks of disease due to *A. salmonicida*, IPNV or SPDV during the field study, routine screening indicated a degree of infection pressure from IPNV and from SPDV, against which the AquaVac PD3 group compared favourably with the positive control group.

In addition, a further GCP-standard, combined safety and efficacy field study at a different European country involving vaccination of Atlantic salmon with the larger combination vaccine AquaVac PD7 (which contains the same antigenic components and adjuvant as AquaVac PD3, however AquaVac PD7 contains additional antigenic components) was presented in support of the efficacy in the field. This approach was considered acceptable in accordance with the principles of the Guideline on the requirements for combined vaccines and associations of IVMPs (EMA/CVMP/IWP/59418/2010). The positive control group in the study received a vaccine containing the same components of AquaVac PD7 except that it lacked an SPDV component, thus serving as a negative control group for SPDV. At one of the study sites, an outbreak of pancreas disease occurred. While mortality during the outbreak was moderate to low, mortality was lower in the AquaVac PD7 group compared to the control group.

Overall, although no natural challenge from *A. salmonicida* occurred during the studies, the data from the field trials provided a degree of further support for the efficacy of the IPNV and SPDV components of the vaccine.

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 benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI POST-AUTHORISATION ASSESSMENTS

Note: not all variations are to be listed here, only those that materially affect the content of the original Public Assessment Report.

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 HPRA website.

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.

Changes:
None.